VOL. XV. No. 1 JANUARY, 1953

BRITISH HEART JOURNAL

UNIVERSITY OF MICHIGAN
FEB 17 1953
MEDICAL LIBRARY

EDITOR
MAURICE CAMPBELL
ASSOCIATE EDITORS
K. SHIRLEY SMITH TERENCE EAST
APPOINTED BY THE BRITISH CARDIAC SOCIETY

CONTENTS

PAGE

First European Congress of Cardiology 1

Coagulation Time in the Selection of Cases for Anticoagulant Treatment. By A. A. FITZGERALD PEEL 8

The Role of the Nervous System in the Maintenance of Pulmonary Arterial Hypertension in Heart Failure. By D. HALMÁGYI, B. FELKAI, J. IVÁNYI, T. ZSÓTÉR, M. TÉNYI, AND ZS., SZŰCS 15

The Effect on the Human Third Heart Sound of Variations in the Rate of Filling of the Heart. By A. W. SLOAN AND MARY WISHART 25

Rheumatic Pericarditis. By G. T. THOMAS, E. M. M. [illegible]TERMAN, AND A. HOLLMAN. 29

Biopsy of the Left Auricle in Mitral Stenosis. By J. B. ENTICKNAP 37

The Mechanism of Effort Syncope in Primary Pulmonary Hypertension and Cyanotic Congenital Heart Disease. By SHEILA HOWARTH AND J. B. LOWE 47

Mitral Incompetence. By WALLACE BRIGDEN AND AUBREY LEATHAM 55

The Electrocardiogram During Angiocardiography. By GEOFFREY REYNOLDS 74

The Lung Volume in Hyperkinetic States. By D. G. B. RICHARDS, A. C. W. WHITFIELD, W. M. ARNOTT, AND J. A. H. WATERHOUSE 83

Potassium and the Cardiographic Changes in Diabetic Acidosis. By C. B. HENDERSON 87

The Effect of Digitalis on the Normal Electrocardiogram. By M. TILIAKOS 98

Ischæmic Heart Disease and Peripheral Occlusive Arterial Disease. By LAWSON MCDONALD 103

Abstracts of Cardiology 108

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

PUBLISHED QUARTERLY SUBSCRIPTION 42/- PER ANNUM. U.S.A. $10.00

EDITORIAL BOARD

APPOINTED BY

THE BRITISH CARDIAC SOCIETY

C. W. CURTIS BAIN, HARROGATE
D. EVAN BEDFORD, LONDON
WILLIAM EVANS, LONDON
A. K. GILCHRIST, EDINBURGH
R. T. GRANT, F.R.S., LONDON
ROBERT MARSHALL, BELFAST
SIR JOHN PARKINSON, LONDON
EDITOR, *British Medical Journal*

NOTICE TO CONTRIBUTORS

Papers dealing with the heart or circulation are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal, and are subject to editorial revision. Contributions should be sent to:

Dr. K. Shirley Smith,
122 Harley Street,
London, W.1.

A summary of the author's observations and conclusions must be given. A paper describing a single case will only be accepted if there are features of unusual importance, or if a line has been made the subject of special observations.

Papers sent for publication must be typed as concisely as possible with double line spacing and a good margin of not less than 1½ inches. Only recognized abbreviations, e.g. cm. or lbs. should be used in the text. Manuscripts should be carefully revised, as alterations in print are costly and apart from slight corrections will be charged to the contributor. The author whose name comes first will receive one proof in page.

Illustrations must be on separate sheets, ready for reproduction, except that on figures lettering which is written in pencil will be replaced by printer's type without charge. These should be on Bristol board or stout, smooth, white paper. The lettering on electrocardiograms should be done in ink and they should be mounted ready for reproduction. Photographs should be printed on glossy paper.

Where there are several electrocardiograms, only a few complexes should be shown, and should be mounted together, and their total width should not exceed 5 inches, or at the most 5½ inches, unless they can be reduced in size.

References to papers in the text should be made by the name of the author and the year, with or without brackets. At the end of the paper they should be arranged alphabetically as below, according to the Harvard system.

Author's name, Initials, Year, Journal (abbreviated according to the World List of Scientific Periodicals), Volume number, Page number, e.g.

Cowan, J. (1929). *Quart. J. Med.*, 22, 237.

Twenty-five reprints will be given to the author or divided among the authors on giving notice when the proof is returned. Further reprints, if desired, may be obtained from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

The annual subscription, 40/- per annum, is payable to the British Medical Association.

Applications for advertisement space should be made to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1.

PROFESSOR LAUBRY SIR JOHN PARKINSON PROFESSOR NYLIN

OPENING OF FIRST EUROPEAN CONGRESS OF CARDIOLOGY

September, 1952

FIRST EUROPEAN CONGRESS OF CARDIOLOGY

OPENING OF CONGRESS WEDNESDAY, SEPTEMBER 10, 1952

SIR JOHN PARKINSON, Chairman of the Congress, announced:

We are honoured to receive a message of welcome from HER MAJESTY THE QUEEN.

Her Majesty hopes that the deliberations of the Congress may indeed be fruitful.

Sir John then gave the Chairman's address.

Ladies and Gentlemen,

It falls to me to take the Chair at the opening of this the First European Congress of Cardiology, and in the name of the British Cardiac Society of which I am President, I extend to all members of Congress a warm welcome to Britain.

The original move towards the formation of a European Society of Cardiology came from Professor Nylin of Stockholm who is now its President and President of this Congress. Under the auspices of the Belgian Society of Cardiology it was founded in January, 1949, and during the first International Congress of Cardiology so brilliantly staged in Paris by the French Society in September, 1950, the opportunity was taken to elect the Council and complete the constitution. It becomes the European counterpart of the successful Inter-American Society, and together these two will form the strongest components of the International Society of Cardiology which is planning the second International Congress to be held in Washington in 1954.

You will notice, however, that Europe and America so combined will fall far short of a world union. Already there are Australasian, South African, and Indian Societies; and we envisage similar representation of Ceylon, Japan, and eventually—with happier relations—of Czecho-Slovakia, Poland, and of Russia and China. There should be a world-wide organization working in harmony for the progress of cardiology, this large section of medicine that deals with the prevention and treatment of diseases of the heart and blood-vessels perhaps the most widespread of all the ills of mankind, and certainly the leading cause of death.

Medical science is not really divided by specialism; it multiplies by division and so retains both its tradition and its vigour. This assembly is composed of physicians who come from twenty European countries and whose main purpose is the advancement of cardiology in its widest sense.

We note with satisfaction and pride how many famous physicians distinguished for their research and teaching in cardiovascular disease are assembled here from the continent of Europe. There is time to name but a few. From *France* we have, with our Honorary President Laubry, Lian, Soulié, Lenègre, Froment, Heim de Balsac, and we remember with admiration Clerc, Gallavardin, and Giraud.

From *Belgium* come Rylant, Van Dooren, and Lequime, and from *Holland*, Formijne and Snellen. We deeply regret the loss of the late Professor Rasmussen of *Norway*. From *Sweden* with our President Nylin come Biörck and Werkö. *Denmark* sends Warburg.

From *Italy* we are glad to have Condorelli, Agostoni, and Puddu. From *Spain* come Codina-Altes and Trias de Bes, and from *Portugal*, Porto, Cabral, and Coelho. *Switzerland* is well represented by Mahaim, Duchosal, and Holzmann.

From *Germany* we have an important deputation including Wollheim and Matthes, and we earnestly desire to renew contact with these fellow workers and others from *Austria*. From further afield we receive among the representatives of *Greece*, Vatsineas, of *Yugo-Slavia*, several delegates, of *Turkey*, Garan, of *Israel*, Münz, and of *Egypt*, Mohamed Ibrahim.

We are highly gratified to have as delegates from the *United States* the President of the American Heart Association, Irving Wright, and its Secretary, William Bunn. Robert Levy and de la Chapelle are here from New York, and Feil comes from Cleveland. We rejoice, especially our surgical members, in the presence of such eminent cardiac surgeons as Crafoord and Santy.

I ask you personally to convey to the ladies accompanying members our friendly salutations and our delight in having them in London with us.

Members of the British Cardiac Society are eager to form and strengthen friendships with colleagues from the continent as far as language permits. We are fellow-Europeans meeting to promote defence—against disease. None should be content to lose his identity in this gathering, but should treat every fellow member as a friend. To this end, I beg each member of Congress to display clearly his name badge at all sessions and social functions, including dinners. I feel sure that our President, Nylin, would like to see all us corpuscles " labelled," *globules marqués*.

A further request is made to all speakers at the scientific sessions to be brief so that they do not take the time allotted to subsequent speakers; and to speak clearly and loudly remembering that they address a European audience.

There was a time, in my memory, when heart disease was regarded with unreasonable fear by the public; they had false notions about its immediate mortality and felt that it was hopeless. The profession itself was unsure in diagnosis and dispirited about treatment. Now, as a result of modern research over these later years, the attitude has changed; indeed we are nearing the time when two physicians from different lands, consulted by a patient, will reach the same diagnosis, give the same prognosis, and prescribe the same sound treatment.

My main function today as Chairman is to welcome on behalf of British cardiologists every single member from abroad. We discard the word foreigner and greet you as friends and colleagues having the same interest and noble purpose, the advancement of our great branch of medicine.

Thanks to rapid progress in our art and science, new hope has arisen. Some heart disease can be prevented, a portion can be alleviated or even cured by surgery, and most will respond considerably to medical treatment. We are encouraged by the unceasing advances of recent years and we meet together in good hope, convinced that scientific progress, with good fellowship combined, will ensure the success of this Congress.

Sir John Parkinson. The time has come for me not to introduce but to present to you in all honour the illustrious master of European cardiology and President of the International Society of Cardiology, our well-beloved CHARLES LAUBRY, and to invite him to address us.

Professor Charles Laubry. Mes amis Parkinson et Nylin m'ont exprimé leur désir de me voir prendre la parole dans cette séance inaugurale. J'en ai été surpris et flatté.

J'ai été surpris, parce que, en tant que Président d'honneur de notre Société, je me croyas nanti du privilège de l'honorariat ou pour mieux dire de l'éméritat, titre qu'on décernait autrefois à Rome aux vétérans et qui leur conférait le droit, du haut de leur passé, de contempler sans s'y mêler les vaines agitations terrestres.

Au fond, je suis flatté et même heureux. Tout d'abord, j'ai le plaisir de saluer le grand Médecin qu'est Sir John Parkinson, de lui dire, qu'à l'abri de son nom, de son autorité, de son aménité qui lui ont valu une admiration respectueuse et unanime, nos séances ne peuvent se dérouler qu'avec succès et profit. Puis, je saisis avec joie l'occasion de féliciter mon collègue et ami Nylin, l'actif Président de la Société inter-européenne de Cardiologie, ce solide groupement que nous avons tenu tous deux, Nylin et moi, sur les fonds baptismaux et qui donne aujourd'hui la mesure de son épanouissement.

Je constate également, avec satisfaction, qu'un de mes voeux, exprimé au Congrès mondial de Paris en 1950, s'est réalisé et que la Cardiologie allemande, par le nombre de ses fidèles, par la notoriété d'un de ses représentants qui préside à sa Société nationale, mon collègue au Comité

international de Cardiologie, le Pr. Wollheim, a pris parmi nous le rang qu'elle mérite. A ces souhaits de bienvenue adressés à nos nouveaux adhérents, je me permettrai de joindre une confidence. Je suis de ceux qui situent la science et en particulier, cette science appliquées qu'est la médecine, en dehors de toute idéologie humaine. Je pense que nos Assemblées doivent être le reflet de cette communion des esprits qui plane au dessus des intolérances des partis. Voilà pourquoi j'ai toujours désiré, pourquoi je voudrais, que l'exemple donné par l'Allemagne fut suivi; que d'autres ralliements se fassent et qu'ainsi, à l'instar de leur grande soeur aînée américaine, on puisse dorénavant parler d'une Société paneuropéenne de Cardiologie.

En évoquant la Société panaméricaine, dont je maintiens le titre de soeur ainée, vous ne comprendiez pas que j'omette de rappeler qu'elle fut notre initiatrice; que, pour cette raison et pour bien d'autres, elle a droit à notre gratitude; qu'enfin, en ce moment même, elle termine à peine ses assises régulières et qu'elle peut encore recevoir notre cordial salut.

Ainsi dorénavant, chacun des deux grands continents, par l'organe de ses Assemblées plénières, a le droit et la mission de réfléchir et de discuter séparement sur la Cardiologie. Nul doute que les représentants de notre vieux continent, qui traîne avec lui un long passé de traditions dont il a la garde, ne sauraient me tenir rigueur de leur en signaler quelques unes.

N'est-il pas utile, par exemple; de souligner une fois de plus que les spécialisations qui sont la marque de notre époque, et parmi elle la cardiologie qui est notre raison d'être, ont besoin d'une surveillance et d'une révision périodiques? A force d'être l'objet d'une curiosité de plus en plus concentrée et satisfaite, la cardiologie semble perdre de vue la médecine générale et amenuiser, sinon trancher, le cordon ombilical qui la rattache à celle-ci et qui lui assure vie et grandeur.

Et dès lors, cette médecine elle même, cette mère nourricière, il ne faudrait pas qu'elle fût troublée dans sa force et dans son allure par les enfants qu'elle allaite. Il ne faudrait pas qu'elle fut, comme eux, entièrement infidèle à quelques traditions impératives. Je me suis déjà prononcé à cet égard et j'étais bien décidé à garder le silence, afin de ne pas rééditer l'image du vieux " *rêveux* " qu'a si bien tracée notre Rabelais; Mais une voix qui m'est chère, une voix plus èloquente et plus jeune que la mienne, celle du Pr. Marañon, a jeté, de son côté, un cri d'alarme. Je manquerais à mes devoirs si je ne lui faisais pas écho et si, parmi les tributs qu'il a dénoncés et qui tendent à peser de plus en plus sur la médecine, je n'en choisirais pas deux pour les dénoncer avec lui et qui semblent intéresser la cardiologie. Ce sont:

D'une part, le *dogmatisme technique* aussi dangereux, pour la saine pratique de notre art que le dogmatisme pseudo-philosophique d'autrefois; d'autre part, le *culte passionné* et souvent exclusif des méthodes scientifiques, que l'on qualifier, à bon droit de " scientificisme." Certes, il est utile pour la précision des données, mais il est périlleux pour l'esprit de réflexion et d'observation prudent qui est celui de la médecine. Il imprime, en effet, à nos esprits, une tendance fâcheuse à des affirmations intransigeantes. Il supprime une certaine politesse intellectuelle qui doit mettre une sourdine à nos jugements. Il installe une foi intolérante qui chasse le *doute*.

Or, à nous autres médecins, que remuent les phénomènes mouvants et complexes de la vie, de la vie normale et pathologique, le doute est utile; il est nécessaire. Je n'entends pas, par là, me faire le champion d'un scepticisme aussi dangereux et stérilisant que les affirmations catégoriques. Je parle du doute salutaire. Il laisse toujours une porte ouverte à l'intervention des forces inconnues qui se meuvent sous le couvert des apparences et ce doute ne détruit pas la confiance hippocratique dans la sagesse de la nature.

Rassurez vous, MM., ce doute dont je fais l'éloge parce qu'il participe intimement de ma nature professionnelle, ne m'empêchera pas d'écouter avec attention vos savantes communications et de leur prodiguer les éloges mérités.

Sir John Parkinson. I will now call upon the President of the European Society of Cardiology, and our President at this its first Congress. By his leadership in research and teaching, and by his nobility of character, he has won our admiration and attained world-wide fame. He will address the assembly and then open the Congress: PROFESSOR NYLIN.

Professor Nylin. Chairman Sir John Parkinson, Honorary President, Monsieur Laubry, Organizing Committee of the Congress, Members of the European Cardiological Society—We Europeans, who are met here to-day to discuss the common interests of our profession, are doubly grateful to Britain. The contribution of British cardiologists obliges us to honour not only the fame of their forebears but the achievements of the present generation. I shall not give, and could not have given you, an exhaustive exposition of the history of the subject. I shall only touch on some significant contributions made by British scientists and physicians.

All research is in some way governed by the age. We may say that, on the whole, cardiology has followed the same course in the various European countries. Unhappily, we must admit that many discoverers have suffered the usual fate of pioneers in being ignored by their contemporaries. Sir James Mackenzie has well said that there are three stages in the history of every medical discovery: " When it is first announced, people say, ' It is not true.' Then, a little later, when its truth has been borne in on them, so that it can no longer be denied, they say, ' It is not important.' After that, if its importance becomes sufficiently obvious, they say, ' Anyhow, it is not new.' "

Now let us contemplate the historical picture.

It was through the discoveries of the Belgian anatomist Vesalius that exact medical science was founded. It was the Englishmen Francis Bacon and Thomas Sydenham who blazed the trail for a critical analysis of the functions of the organs, as well as for pathological anatomy and the classification of diseases. Servetus, Columbus, and Cesalpino made tentative efforts to trace the circulation of the blood, but this field of research was first illumined by Harvey's classic and splendid contribution. We have just enjoyed the privilege of listening to an exposition from our " grand old man " and great authority on Harvey, Professor Charles Laubry. I mention Harvey's name with that deep veneration which he inspires in all of us.

A hundred years after the appearance of Harvey's immortal work, *De Motu Cordis*, Stephen Hales published his *Statical Essays: containing Hæmastaticks.* Truly a remarkable work from the pen of this highly gifted cleric and universal student. In spite of their shortcomings, his experiments with animals constitute an introduction to the physiology of circulation. Not only did he measure the pressure in the femoral artery of a mare, but he also attempted to determine the diastolic filling of the heart, as well as the speed of the circulation. I have searched Stephen Hales's original works in vain for any reference to his great forerunner, Harvey; he does, however, quote Leeuwenhoek; and he discusses the function of the red corpuscles.

British contributions to physiology have been of great importance to the various branches of modern medicine, especially with regard to the circulation of the blood. It was the physiologist, Starling, who, in his Linacre Lecture on the Law of the Heart in 1918, nearly 200 years after Stephen Hales, presented the first detailed study of the diastolic filling of the heart, and its relation to the heart's stroke volume. This relation has, since Starling, always been the subject of keen study; it is deemed to be of fundamental importance to the understanding of the heart's action, from the point of view of both physiology and clinical medicine. In recent times, modern radiological and physiological methods of ascertaining the heart's volume and its minute and stroke volume, in the case of the living man, confirm some of Starling's conclusions from experiments on animals. It was in this field that McMichael and his school made their especial contribution towards elucidating the effect of digitalis in heart failure.

About 1770, the element of oxygen was discovered at about the same time in England and Sweden, and was given the sensational name of " life-gas." Priestley, its English discoverer collaborated with Thomas Beddows, and with none other than James Watt.

In 1923, the English physiologist, A. V. Hill, received the Nobel prize for physiology and medicine on the strength of his pioneer work in investigating muscular heat. In this connection, he made a close study of oxygen consumption, which was of great significance to cardiology. J. S. Haldane and Sir Joseph Barcroft, too, have indirectly enriched our cardiological knowledge by comprehensive researches into hæmoglobin, the oxygenation of the blood, and the body's " call for oxygen," as Barcroft describes it.

In his work on the action-currents of the heart, published in 1887, the English physiologist Waller made a notable contribution to cardiology. Certainly, it was the Dutch Nobel prize-winner Einthoven who made it possible to apply electrocardiography to clinical medicine by his string galvanometer. But this nowise detracts from Waller's great achievement. Einthoven was the first to acknowledge his great debt to the Englishman, Sir Thomas Lewis, when he said, in his speech on receiving the Nobel prize: " I doubt whether, without his precious contribution, I should have the privilege of standing in your presence here to-day."

Many discoveries in different fields of fundamental research have been applied to new and important questions. One example of these is the Nobel prize-winner, Sir Henry Dale's discovery of the transmission of nerve impulses by acetyl-choline. The atomic era was ushered in by one of the greatest physicists of all time, Lord Rutherford, in his *Radio-activity*, published in 1904. His pupil, the Nobel prize-winner George de Hevesy, introduced the radio-active labelling technique. It was in Sweden, in 1942, that P^{32} was used for the first time for labelling red blood corpuscles in man. It has turned out to have great possibilities of development. It has even been possible, in some measure, to apply it therapeutically, in the use of radio-active iodine, for example. It is probable that, especially in the field of the circulation of the blood, we stand on the threshold of a new age of discovery.

In the eighteenth century, the botanist was still often a physician, and the physician a botanist. In the latter part of the century, William Withering appeared. Every physician of our generation, all over the world, prescribes digitalis almost daily, and it is remarkable that, broadly speaking, we still use the same preparation, follow the same indications, and give the same dose of digitalis. Withering was an uncommonly skilful botanist; he was in touch with pupils of Linnæus, and published the first book on the British flora. It was, therefore, no accident that Withering surmised that, in the wise women of Shropshire's decoction of a score of herbs, digitalis was the most efficacious ingredient. In his classical work, published in 1785, *An Account of the Foxglove and some of its Medical Uses, with Practical Remarks on Dropsy*, he tells us that the recipe had long been kept a secret " by an old woman in Shropshire, who had sometimes effected cures after regular practitioners had failed." It is curious that the portrait of Withering which is often reproduced was painted by the Swedish artist, Fredrik von Breda, a pupil of Sir Joshua Reynolds.

To be, like Withering, both a physician and a scientist is vouchsafed to few. To be a physician only is indeed a great and difficult art. A good doctor must be a good psychologist, a man of swift observation, critical skill, and active sympathy. Englishmen have always been known as skilled and kindly doctors, and it is characteristic that a recent book on Sir James Mackenzie bears the title, *The Beloved Physician.*

A prominent contemporary of Withering was the London physician, William Heberden. He was a leading member of the Royal College of Physicians of London, of whose transactions he may be called the founder. He was the first to present, about 1768, a clinical picture of angina pectoris. After his death, his son published his father's collected works, under the title of *Commentaries on the History and Cure of Diseases.*

The English school had the honour of contributing to our medicine chest for the treatment of angina pectoris two highly important remedies. In 1867, when he was only 23 years old, Lauder Brunton described his remarkable experiments with amyl nitrite. William Murrell, a contemporary of his, possessed of both pharmacological and physiological training, introduced a remedy unsurpassed even in our own day, nitro-glycerine.

In Britain, at the beginning of the nineteenth century, the development of cardiology is characterized by clinical experience, deep knowledge of symptoms, and especially physical findings. The Irish school is represented by Cheyne, Adams, Graves, Corrigan, and Stokes, who have all given their names to different pathological circulatory conditions. The prominent English clinicians, Parry, Latham, Hope, Peacock, Gibson, and Gaskell, are protagonists of this era in cardiology. In 1907, Sir Arthur Keith and Martin Flack published their classical discoveries concerning the sino-auricular node.

At the end of the nineteenth century, a giant in English cardiology arose. This was Sir James Mackenzie. He was a forceful personality, whose keen intellect was balanced by a strong sense of responsibility and close sympathy with his patients. Besides this, Mackenzie took a passionate interest in scientific work. Perhaps his most precious contribution to it was the ink polygraph, by means of which, among other things, he did much to elucidate the arrhythmias of the heart. Mackenzie's career was amazing and was surrounded by a halo of romance. He was deeply interested in his pupil, Sir Thomas Lewis's investigations with the aid of electrocardiography which both confirmed and further illumined what Sir James had himself observed through his ink polygraph. Though he well understood the importance of modern technique in diagnosis he did not fail to emphasize the value of accurate observation at the sick-bed. The following story is told of a foreign colleague, who wanted to meet " The Great Mackenzie." The visitor talked enthusiastically about electrocardiography, and descanted profusely on the Q wave. At last, after Mackenzie had been silent throughout, the foreigner said: " What line of research would you advise me to take up when I go home? " Mackenzie replied: " I should advise you to go into general practice and stay in it for ten years."

Sir James surrounded himself with a group of men prominent in medicine, such as Sir Arthur Keith, Sir William Osler, and Lord Dawson of Penn. Sir Thomas Lewis did much to further the development of cardiology through his physiological, patho-physiological and clinical observations. Sir John Parkinson's achievements also, which were of extraordinary importance to clinical cardiology, are clearly avouched by Wilson's words: " Mackenzie glowed with pride in the great reputation of his disciple and friend, Sir Thomas Lewis, and the same affection went out to Dr. John Parkinson, his assistant and successor at the London Hospital. They were like father and son, and what John was doing, was always of eager interest to his chief." After Sir James's death, Sir John Parkinson collaborated with Bedford, and it is to them we owe some of the pioneering achievements in coronary diagnosis.

British cardiologists of to-day have paid glowing tribute to the labours of their illustrious forerunners and have supplemented them. Such men as Sir John Parkinson, Bramwell, Bedford, McMichael, Campbell, Wood, Evans, Grant, Shirley Smith, and Gilchrist have enriched modern cardiology with notable contributions, recognized throughout the world.

The European Cardiological Society tenders its heartiest greetings to the British Cardiac Society on the opening of the first European Cardiological Congress. We are especially grateful to our generous hosts for inviting us to assemble here, and for taking on themselves the heavy burden of organizing this congress. We are all convinced that, through this congress, we shall contribute substantially to the progress of cardiology. As a proof of our high appreciation of British cardiology, with its proud and honourable traditions, and in homage to its venerable representative, I ask you, in the name of the European Cardiological Society, to appoint Sir John Parkinson Honorary President.

I now declare the Congress open.

The Scientific Programme of the Congress was printed in the British Heart Journal (1952) 14, 547, and reported in the Lancet (1952) 2, 575, and in the British Medical Journal (1952) 2, 657.

At the concluding banquet on Friday, September 12, *Sir John Parkinson* spoke as follows:

Ladies and Gentlemen,

So far as I can judge, this Congress has been justified both by the scientific advances recorded at our meetings, and by the friendly spirit which has developed among all members of the twenty countries of Europe here represented.

To-night is an opportunity to voice the thanks we owe to those who have helped in the organization of this Congress. The University of London not only placed their central halls at our disposal

but the authorities have acted throughout with courtesy and kindness. The Royal College of Physicians has shown great hospitality, and so has the British Council and the Ciba Foundation.

As Chairman of the Congress Committee, Evan Bedford has taken upon himself the largest share in planning the Congress and has proved himself a great organizer and a staunch upholder of the interests and rights of European Cardiology. We offer him our cordial thanks.

We are thankful to each member of the congress committee, Crighton Bramwell and Paul Wood, and especially to Maurice Campbell, Editor of the *British Heart Journal*, who has worked long and late on the scientific communications, and whose experience and judgment have been invaluable. Oram has been most helpful in many ways. To Jenner Hoskin, and also to Mrs. Jenner Hoskin, we owe much for all the trouble they have taken to plan and carry out the social arrangements. Many other helpers are unnamed, but we are grateful to them.

Shirley Smith has shown himself to be the ideal Secretary, imperturbable and tireless; he has been notably successful in his heavy and endless duties to which he has devoted a great part of his time for many months; we applaud him!

To-night we of the European Society of Cardiology are honoured by the presence of a few invited guests, and they are most welcome. Foremost among them by virtue of his national office and by the esteem he has gained from the profession in Britain, is the Minister of Health, the Right Honourable Iain Macleod. With him is the Chief Medical Officer, Sir John Charles, in whom the profession has such complete confidence. The University of London is well represented by Dr. Logan, the Principal, who embodies the spirit of university life applied to life in London. Sir Russell Brain as its President has always expressed admirably the youthful vigour and importance in our national life of the venerable Royal College of Physicians. We are pleased to have with us two distinguished editors—Dr. Fox of the *Lancet*, and Dr. Clegg of the *British Medical Journal*.

Those are the selected guests of the European Society. As this is the dinner of the Society itself I will only say how proud we are to have here among its members such famous masters in European Cardiology as Laubry, Nylin, Lian, Warburg, and Condorelli and as visiting members such distinguished American cardiologists as Irving Wright and Robert Levy.

I would now renew the welcome extended by the British Cardiac Society to the continental members of the European Society. After all, its future depends mainly upon the loyalty of each member to his own national society.

We have been highly gratified by the way you have mixed so naturally and cheerfully with us. It has been good to be with you, and we shall never forget your visit. In future when you come to England you should feel that you have friends here; that is what we should like to be a happy sequel of this great gathering.

You seem to have pardoned our shortcomings; we could not hope to compete with the brilliance of the international gathering in Paris in 1950, or with that which awaits us in Washington in September, 1954, when we Europeans look forward to joining our American colleagues in the next assembly of the cardiologists of the world.

Finally, let us hope that the advances recorded at such a congress as this will be continued and solidified so that we may offer our fellow men and women, and children, larger protection from the causes of heart disease, greater relief, and better prospect of cure.

COAGULATION TIME IN THE SELECTION OF CASES FOR ANTICOAGULANT TREATMENT

BY

A. A. FITZGERALD PEEL

From the Victoria Infirmary, Glasgow

Received June 12, 1952

Anticoagulant therapy in cardiac infarction has raised several new problems. Its efficacy in reducing both mortality and complications appears to be beyond doubt. Tulloch and Gilchrist (1950) summarized the results in eleven earlier series and added their own figures : anticoagulants reduced the mortality from 29 to 15 per cent. The incidence of thrombo-embolic complications rose from 11 per cent before 1940 to 28 per cent between 1945 and 1948 ; these occurred in 28 per cent of Tulloch and Gilchrist's control cases but in only 13 per cent of their treated group. On the other hand anticoagulant therapy has disadvantages. Tromexan and dicoumerol necessitate frequent laboratory tests and few patients can be treated at home, thereby increasing the demands on hospital accommodation. Heparin is expensive and requires frequent intravenous injections ; the efficacy of intramuscular injections has yet to be proved.

The mortality figures show that 15 per cent of patients with cardiac infarction will die and 71 per cent will recover whether anticoagulants are given or not ; in 14 per cent anticoagulants may save life. Similarly they prevent complications in 15 per cent of cases. A maximum figure of 29 per cent includes all these for whom anticoagulants are essential ; for the rest they are immaterial. The first problem is to differentiate those who require anticoagulants from those who do not.

A second problem concerns their use in cardiac ischæmia without infarction and in the " slight coronary attacks " of Papp and Shirley Smith (1951, *a* and *b*). These authors state that " anticoagulant treatment is not indicated since the risk of thrombo-embolic complications or extension of infarction is so slight," but continue : " Further thrombosis in major coronary branches must remain an ever existing danger." Cases that start as a " slight coronary attack " but later develop the picture of severe infarction are by no means rare, and in this group also, anticoagulants are sometimes essential but often unnecessary.

Finally Mounsey (1951) has re-emphasized the well-known prodromal symptoms that occur in some cases of cardiac infarction. Post-mortem evidence suggested different pathological processes as the cause of the prodromal symptoms. In one case they were attributed to incomplete occlusion of a vessel by a thrombus, in one to hæmorrhage into an atherosclerotic plaque, and in one to progressive atheromatous narrowing. These pathological findings suggest that anticoagulants are essential in some cases, dangerous in some, and immaterial in others. Papp and Smith (1951, *c*) now advocate anticoagulants in this prodromal coronary syndrome.

The aim of this paper is to differentiate those patients in each of the foregoing groups who must, from those who need not, be given anticoagulants. As far as I am aware this has not been tried. A personal attempt to base the selection on clinical grounds made during 1950 met with complete lack of success. Selection for anticoagulant treatment might reasonably be based on tests of blood coagulability. Ogura *et al.* (1946), using Waugh and Ruddick's (1944) " heparin tolerance test," showed that acceleration of clotting occurred after a cardiac infarction in 78 per cent of their cases. It commonly appeared on the third day and lasted for three weeks, occasionally persisting for four or five weeks. The authors made the important observation that extension of the original

infarct and thrombo-embolic complications only occurred at a time when acceleration was present ; they assume that once it has developed, the acceleration may lead to further complications.

The Waugh-Ruddick test involves a number of tubes with differing dilutions of blood and heparin ; it is essentially a laboratory test, ill adapted for use in a patient's home. Rosenthal (1949) introduced a modified and simplified test requiring only a single tube : the result remained reasonably constant with successive determinations in normal controls ; bed rest and digitalis each caused acceleration. Eight of his eleven cases with prolonged times had clinical evidence of hæmorrhage, and he implies that the reverse is equally likely to be true. This seemed a hopeful test for selection of cases for anticoagulant treatment. Since the beginning of 1951 it has been used in all cases of cardiac infarction, in " slight coronary attacks," in patients with recent onset of coronary pain, and in those whose former coronary pain had changed in behaviour or intensity.

The Heparin-retarded Coagulation Time (*HRCT*)

Rosenthal's (1949) technique has been modified in one important respect. He specifies rubber-stoppered glass test tubes of 13 mm. bore and 7·5 cm. length; we have used tubes of 7 mm. bore. The tubes are marked at a level corresponding to 1·1 ml. fluid ; 0·1 ml. isotonic saline solution containing 0·004 mg. heparin is placed in each tube. For the test, blood is added up to the 1·1-ml. mark, the stopper is inserted, and the contents are mixed by inverting the tube several times. The end point is reached when the tube can be inverted without any fluid breaking away. To prevent contamination with tissue fluid, suction should be avoided during venipuncture until the needle has entered the vein ; and the tube should be filled from the middle of the syringe, the first and last blood to enter it being discarded.

The bore of the tube affects the result. In a narrow tube a surface clot develops before the entire contents are solid ; if the blood has a high sedimentation rate the sedimented corpuscles can be seen to flow on inversion for some time after the surface has solidified. In a wide tube the centre of the surface is the last part to clot and the tube cannot be inverted until the entire contents are solid. Observations with narrow and wide tubes filled from the same syringe show that the end point is always shorter, and often much shorter, in the narrow tube. The figures that follow refer to results obtained with narrow tubes. The test has many other technical defects. The end point is often very gradual and rarely sharp. Excessive shaking seems to retard coagulation. The time elapsing between venipuncture and mixing of the blood with heparin probably influences the result. Contamination of the blood with tissue fluid provides another possible source of error. Despite its defects, the test has differentiated several broad groups.

TABLE I

THE HEPARIN-RETARDED COAGULATION TIME IN CONTROLS, IN THROMBOPHLEBITIS, ETC., IN CARDIAC INFARCTION, AND IN THE CORONARY PRODROMAL SYNDROME*

	Heparin-retarded coagulation time in minutes				
	Accelerated 5–9	10–16	Borderline 17–19	Normal 20–40	Prolonged Over 40
Non-thrombotic conditions 32	0	3	5	23	1
Thrombophlebitis, embolism, etc. 8	2	2	0	4	0
Cardiac infarction 88	11	26	11	35	5
Coronary prodromal syndrome and cardiac ischæmia 61	8	12	4	36	1

* No anticoagulant had been given prior to the test.

Rosenthal gives the normal clotting time as between 20 and 36 minutes. Personal experience in control cases suggests that with the narrower tubes the lower limit of normal is 17 or possibly 16 minutes (Table I). A figure of 16 minutes was obtained in two cases of gallstone colic ; a shorter clotting time of 13 minutes was only encountered once.

Of 88 patients with cardiac infarction 48 (55%) had an *HRCT* of less than 20 minutes and 37 (42%) of less than 17 minutes. Contrary to the report of Ogura *et al.* (1946) figures as low as 5 to 10 minutes have been obtained as early as the first day (Table II). There can be little doubt of the urgent necessity for anticoagulants in these cases. In some cases the *HRCT* has been normal during the first day or two but has become accelerated later. Acceleration is frequent in the first three weeks and occasionally persists beyond the fourth week. In another group the *HRCT* has remained within the normal range throughout the attack. Finally, a few patients had a prolonged

TABLE II

THE *HRCT* AT DIFFERENT TIMES AFTER THE ONSET OF CARDIAC INFARCTION.*

Day of disease	No. of tests	Heparin-retarded coagulation time in minutes: Accelerated 5–9	Accelerated 10–16	Borderline 17–19	Normal 20–40	Prolonged Over 40
1st day ..	25	4	8	2	9	2
2–3 days ..	13	2	4	2	4	1
4–7 days ..	11	2	1	2	6	0
Total :						
1st week ..	49	8	13	6	19	3
2nd week ..	13	1	3	1	6	2
3rd week ..	10	1	5	0	4	0
4th week ..	4	0	1	0	3	0
Over 4 weeks	8	1	2	3	2	0
Onset uncertain	4	0	2	1	1	0
Total	88	11	26	11	35	5

* No case had received anticoagulants prior to the test.

HRCT which later fell to normal, and in one case became accelerated ; prolongation was only found during the first two weeks. Of 61 patients with cardiac ischæmia or coronary prodromal syndrome 24 (39%) had an *HRCT* of under 20 minutes and 20 (33%) of under 17 minutes (Table I).

The following serial observations are of interest. A man of 43, previously healthy, wakened with severe cardiac pain which lasted three hours ; he spent two weeks in bed and was referred on the 19th day. He was then symptom-free but his cardiogram showed an anteroseptal infarct and his *HRCT* was 15 minutes. On the last day of a three-weeks' course of tromexan his *HRCT* was 40 minutes ; two days later it was 24 and on the following day 8 minutes. Two days after this he had a second attack of severe cardiac pain lasting 16 hours ; when next seen a week after the second attack his *HRCT* was 22 minutes. This case suggests that extension of thrombosis is likely when the *HRCT* falls. It is possible that in consequence of thrombosis some constituent of blood is used up, leading to a rise in *HRCT* until the deficiency has been made good. The normal or prolonged *HRCT* sometimes found a day or two after the onset might be explained on this basis.

A man of 50 with thrombo-angeitis obliterans presented with a migrating thrombophlebitis of two months' duration ; he had a fresh thrombotic lesion and his *HRCT* was 23 minutes. On the last day of a three weeks' course of tromexan it was 32 minutes and the phlebitis seemed quiescent. The *HRCT* was repeated three days later and thereafter at weekly intervals ; the successive figures were 38, 32, 28, and 23 minutes. At this stage a fresh lesion appeared.

RESULTS OF TREATMENT IN CARDIAC INFARCTION USING THE *HRCT* AS A BASIS OF SELECTION FOR ANTICOAGULANTS

Twenty minutes was arbitrarily selected as the figure below which anticoagulants were given, above which they were withheld. If the *HRCT* was normal on the first or second day, it was repeated daily until the third day and at intervals thereafter ; anticoagulants were given if and when the figure dropped below 20 minutes. Four patients originally placed in the " no anticoagulant

group " were later transferred to the " anticoagulant group " because of acceleration that appeared between the third and twelfth days. The routine anticoagulant used was tromexan ; dosage was adjusted with the aim of keeping the prothrombin time at two and a half times the control figure. Heparin was given as well as tromexan for the first few days if early control seemed important on clinical grounds or because of an alarmingly short *HRCT*. More recently heparin had been given as a supplement to tromexan whenever the prothrombin time is less than twice the control value, whether at the start of treatment or later in the course. Prothrombin estimations were made daily. Heparin alone has not been used in cardiac infarction, but it was used alone in some patients with the coronary prodromal syndrome. Anticoagulant treatment was given for three weeks: the *HRCT* was repeated on the last day of treatment and again two or three days later ; if accelerated at either test treatment was continued or resumed, the tests being repeated at the end of each subsequent week's treatment. In most cases the *HRCT* was prolonged or high normal after three weeks and remained so ; several patients needed a fourth but only two needed a fifth week's treatment.

Table III shows the composition, complications, mortality, causes of death, and frequency of second attacks in 86 cases of coronary occlusion. All had cardiographic signs of cardiac infarction ; those in whom the clinical history suggested coronary occlusion but the cardiogram showed ischæmic changes only are not included in this table, but have been classified and are discussed as cardiac ischæmia.

The most striking findings are in the group of 38 patients from whom anticoagulants were withheld because of a normal or prolonged *HRCT*. Although this group includes 16 severe cases with shock and/or failure, a proportion almost identical with that found among the 48 patients

TABLE III

THE SEVERITY, COMPLICATIONS, MORTALITY, CAUSES OF DEATH, AND INCIDENCE OF SECOND ATTACKS IN 86 CASES OF CARDIAC INFARCTION

	HRCT under 20 minutes. Anticoagulants given	*HRCT* 20 minutes or more. Anticoagulants withheld
Total cases	48	38
Severity :		
Shock or failure present	22=46%	16=42%
Shock and failure absent	26=54%	22=58%
Complications :		
Extension of infarct	4=9%	3=8%
Embolism	5=10%	2=5%
Death :		
Within 4 weeks	6=13%	3=8%
Within 6 weeks	8=17%	5=13%
Cause of death :		
Extension of infarct		
Death from shock	2	1
Death from rupture	1 =8%	0 =5%
Pulmonary infarction	1	1
Cardiac failure	3=6%	2=5%
Ventricular fibrillation	1=2%	1=3%
Second attacks within 6 months :		
Survivors after 6 weeks	40	33
Second attacks occurred in	5=13%	1=3% +1 sudden death

with accelerated *HRCT*, complications were less frequent, the mortality was lower, and second attacks within six months were infrequent. The mortality of 13 per cent in six weeks compares

very favourably with that quoted by Tulloch and Gilchrist (1950) for anticoagulant-treated cases. One death resulted from extension of infarction. This was an early case in the series ; he was seen ten hours after the onset of a severe attack and his *HRCT* was 32 minutes ; the importance of repeating the test on the second and third day was not realized. For a week he progressed satisfactorily but extension of infarction occurred on the 8th and he died on the 9th day. One death occurred from pulmonary infarction : this man was first seen on the 23rd day when his *HRCT* was 35 minutes : the embolism took place two days later and he died on the 31st day. Two deaths were due to cardiac failure, on the 3rd and 13th days : one occurred suddenly in the 5th week from ventricular fibrillation.

Extension of infarction or embolism occurred in 5 cases including the two who died, an incidence of 13 per cent. The corresponding figure for cases with accelerated *HRCT* was 9 out of 48 (19%) despite anticoagulant treatment. Finally, only one of the 33 survivors had a second attack within six months ; whereas five of the 40 survivors in the accelerated group developed second attacks.

The mortality was higher in patients with accelerated *HRCT* (17% in six weeks). Death from cardiac failure and sudden death from ventricular fibrillation occurred with equal frequency and together these caused a mortality of 8 per cent in each group. Thrombo-embolic deaths were more frequent in the accelerated group (8 as compared with 5%). It is felt, however, that three deaths from extension of infarction might have been prevented. In each case tromexan failed to maintain a steady prothrombin time and the latter fell to a totally inadequate level at one stage ; each patient had cardiac pain with extension of infarction later that day ; two became shocked and died within 24 to 48 hours ; the third ruptured her infarct four days later. Since these incidents the prothrombin time has been estimated daily ; supplementary heparin is now given as a routine whenever the figure is below twice the control value, and continued until this level is regained. A fall in prothrombin time has since occurred in several patients ; one had mild transient pain without extension of infarction ; in the others no ill effects followed. It is hoped to eliminate some deaths from extension of infarction by this technique and to reduce the mortality to the region of 10 per cent.

TABLE IV

DEATHS AND THROMBO-EMBOLIC COMPLICATIONS

	Severe attacks with shock and/or failure		Attacks without shock or failure	
	HRCT accelerated	*HRCT* normal	*HRCT* accelerated	*HRCT* normal
Total cases	22	16	26	22
Thrombo-embolic complications	7=32%	3=19%	2=8%	2=9%
Deaths :				
Within 4 weeks	5=23%	3=19%	1=4%	0
Within 6 weeks	6=27%	4=25%	2=8%	1=5%
Cause of death :				
Thrombo-embolic	2=9%	1=6%	2=8%	1=5%
Cardiac failure	4*=18%	3*=19%	0	0
Second attacks within 6 months :				
Survivors after 6 weeks ..	16	12	24	21
Second attack occurred in ..	2=13%	1=8%	3=13%	0 (but 1 sudden death)

* In each of these groups, one death was due to ventricular fibillation.

The most important prognostic features are the presence or absence of shock or failure, with or soon after the onset ; but whether the attack be mild or severe the prognosis is further affected by the *HRCT*. Table IV gives the results separately for cases with and without shock or failure. Deaths from heart failure or ventricular fibrillation only occurred in patients with severe attacks ; but these caused death in almost one-fifth (18%) of such patients irrespective of whether the *HRCT* was accelerated or normal. On the other hand death from extension of infarction or embolism was almost as frequent in mild as in severe attacks, but was more likely when the *HRCT* was accelerated irrespective of the severity. Finally, a recurrence within six months occurred in one of every eight survivors whose *HRCT* was accelerated whether the original attack was mild or severe ; only one recurrence took place among twelve survivors from major attacks with a normal *HRCT* and there were no second attacks among twenty-one survivors from mild attacks with normal *HRCT*.

The frequency of second attacks in the accelerated group despite anticoagulant treatment is disappointing but probably not without significance for prophylaxis. They may develop soon after completion of treatment. Thus a patient was seen on the 26th day after a mild posterior infarct ; his *HRCT* was 10 minutes. It was 18 minutes after three, and 45 minutes after four weeks' tromexan ; four days later it was 35 minutes. A fortnight after this he was readmitted in a second attack with anterolateral extension of the infarct ; his *HRCT* had dropped to 20 minutes. He had a second four weeks' course of tromexan ; three weeks after discharge he was admitted to another hospital in a third attack, details of which are not available. It seems advisable to estimate the *HRCT* at weekly intervals after a course of treatment until a steady level is maintained ; a prophylactic course should be considered if the *HRCT* approaches the danger level. Second attacks have been rather more frequent recently : of 326 survivors during 1928–50, 18 (6%) had a recurrence within 6 months ; of 73 survivors in the present series 6 (8%) had a second attack ; five of them had received anticoagulants because of an accelerated *HRCT*.

The *HRCT* as a Selective Test for Prophylactic Treatment

The test was applied in patients with recent abrupt onset of effort angina, in those with paroxysmal cardiac pain at rest, and in those with prolonged cardiac pain at rest whose 12-lead cardiogram failed to show the QRS changes of infarction. In some the cardiogram was normal, in some it showed ischæmic changes, and in some there were other abnormalities such as left ventricular stress. Anticoagulants were given if the *HRCT* was below 20 minutes. The numbers so far are too small to justify positive claims but the results are encouraging. Of 50 ana!ogous cases in private practice during 1946–50, 10 developed infarction within six weeks, 27 escaped infarction, and 13 remain untraced. Of 51 cases in 1951–52, 3 developed infarction within six weeks ; 27 with accelerated *HRCT* were anticoagulant-treated and provided two infarcts ; 24 with normal *HRCT* received no anticoagulants and yielded one infarct.

Summary

A modification of Rosenthal's " heparin-retarded coagulation time " was used to select cases of cardiac infarction, cardiac ischæmia, and coronary prodromal syndrome for anticoagulant therapy. The technique of the test requires improvement, but it has differentiated cases with acceleration of coagulation time from those with normal or prolonged values. Each group contained an almost identical proportion of severe cases with shock and/or failure.

Cardiac infarction with accelerated *HRCT* had a mortality of 17 per cent despite anticoagulants. Cardiac infarction with a normal or prolonged *HRCT* had a mortality of 13 per cent although anticoagulants were withheld. Deaths from cardiac failure and ventricular fibrillation were equally frequent in the two groups ; thrombo-embolic deaths account for the difference. Second attacks within six months were much more frequent in survivors who had an accelerated *HRCT* and had received anticoagulants.

The *HRCT* is of help in determining the duration of anticoagulant therapy and may indicate the need for prophylactic courses after recovery. Heparin should be given as well as tromexan until the prothrombin time exceeds twice the control value and whenever it falls below this critical level.

Cases of cardiac infarction in which the *HRCT* remains normal may justifiably be treated without anticoagulants ; facilities thus released may be used for prophylactic treatment in prodromal or convalescent cases selected on the basis of the test. The results of prophylactic treatment are regarded as encouraging.

It is a pleasure to express my thanks to Dr. J. Craig for estimating prothrombin times, supervising tromexan and heparin dosage, and carrying out the *HRCT* during and after treatment ; to Drs. J. J. McCall, A. K. Bain, D. D. G. Simpson, and R. I. Alexander, Registrar and Residents respectively, for numerous *HRCT* estimations ; and to many general practitioners whose co-operation has made possible a complete follow up of these cases.

References

Mounsey, P. (1951). *Brit. Heart J.*, **13**, 215.
Ogura, J. H., Fetter, H. R., Blankenhorn, M. A., and Glueck, H. T. (1946). *J. clin. Invest.*, **25**, 586.
Papp, C., and Smith, K. S. (1951, *a*). *Brit. med. J.*, **1**, 1471.
——, —— (1951, *b*). *Brit. Heart J.* **13**, 17.
——, —— (1951, *c*). *Brit. Heart J.*, **13**, 467.
Rosenthal, R. L. (1949). *J. lab. clin. Med.*, **34**, 1321.
Tulloch, J. A., and Gilchrist, A. R. (1950). *Brit. med. J.*, **2**, 965.
Waugh, T. R., and Ruddick, D. W. (1944). *Canad. med. Ass. J.*, **50**, 547.

THE ROLE OF THE NERVOUS SYSTEM IN THE MAINTENANCE OF PULMONARY ARTERIAL HYPERTENSION IN HEART FAILURE

BY

D. HALMÁGYI, B. FELKAI, J. IVÁNYI, T. ZSÓTÉR, M. TÉNYI, Zs. SZÜCS

From the First and Second Departments of Medicine, University Medical School, Szeged, Hungary

Received May 20, 1952

Elevation of pressure in the pulmonary veins, with a consequent elevation of pressure in the pulmonary capillaries and pulmonary artery has for many years been invoked to explain pulmonary hypertension in both mitral stenosis and left ventricular failure. Ignoring the possibility of pulmonary vasoconstriction, this hypothesis was in complete accordance with the " mechanistic " concept of the regulation of pulmonary pressure, emphasized recently by Cournand (1947, 1950) and Hamilton (1951). It was based mainly on the relative refractoriness of the pulmonary circulation towards substances affecting the systemic circulation.

It was soon established, however, that elevation of the pulmonary venous pressure is only partly responsible for the high pressure in the pulmonary artery that is observed in heart failure. Elevation of pulmonary " capillary " pressure beyond the colloid osmotic pressure of plasma causes an increase in the pulmonary pressure gradient (Dexter *et al.*, 1950), as a result of an increase of the pulmonary arteriolar resistance. Lewis *et al.* (1952), emphasize that in mitral stenosis this increased arteriolar resistance is a physiological counterpart to the anatomical changes observed in the small pulmonary arteries by Parker and Weiss (1936) and Larrabee *et al.* (1949). In face of this " static " theory of increased pulmonary arteriolar resistance it seems hard to understand why the presence or absence of heart failure raises or lowers the pressure in the pulmonary artery, presumably without a change in the size of the stenosed orifice (Bloomfield *et al.*, 1949 ; Bayliss *et al.*, 1951), or in the lumen of the " statically " narrowed pulmonary arterioles. Not even an increase of the circulating blood volume explains this apparent contradiction. Nor does the decrease of pulmonary arteriolar resistance following mitral commissurotomy (Draper *et al.*, 1951 ; Dexter, 1952) favour this theory. On the other hand, no corresponding narrowing of the pulmonary vessels can be demonstrated in hypertensive heart failure despite a similar elevation of pulmonary arteriolar resistance (Borden *et al.*, 1950). These data seem sufficient to support the view that anatomical factors alone cannot account for all the increase in pulmonary arterial pressure. The mechanism of this reversible elevation of pulmonary vascular resistance, therefore, needs further study.

Anoxia, by producing widespread vasoconstriction in all parts of the circulation, elevates also pulmonary vascular resistance (Motley *et al.*, 1947 ; Liljestrand, 1948 ; Dirken and Heemstra, 1948 ; Doyle *et al.*, 1951, etc.). Pulmonary hypertension following the administration of histamine was also observed in dogs by Dixon and Hoyle (1930). The vasomotor response to both these stimuli is a consequence of their direct chemical action on the pulmonary vessels. The significance of the nervous system as a source of vasomotor stimuli affecting the pulmonary circuit is generally underestimated. Kuntz (1946) stated that the pulmonary artery and its branches are more richly supplied with nerves than the usual anatomical descriptions and the results of physiological experiments seem to indicate. This statement is corroborated by the observations of Takino (1933),

Larsell and Dow (1933), Gaylor (1934), Hochrein (1938), Daly and Hebb (1942, 1952), Sternberg and Tamari (1928), Pearce and Witteridge (1951), and many others. The circulatory adjustments existing between the pulmonary circuit and the different parts of the systemic circulation (Schwiegk, 1935 ; Parin, 1943–44 ; Puder, 1938, 1942 ; Scherf and Schönbrunner, 1937) offer a good support for the functional importance of the nerve supply of the pulmonary circulation.

The work of Greene and Bunnell (1950) and Fowler *et al.* (1951) seemed to indicate that nervous stimuli may contribute to the pathogenesis of pulmonary hypertension in heart failure, for administration of tetra-ethylammonium bromide resulted in a decrease in the pressure of the pulmonary artery and in the resistance of the pulmonary arterioles.

In face of these confusing data, an attempt was made to clarify the position as follows.

(1) A substance was sought capable of raising the pressure in the pulmonary artery without affecting significantly the cardiac output and the systemic arterial circulation. Histamine and anoxia do not correspond to these requirements because of the confusing number of their effects on the circulation. Investigating the effect of ergotamine in the dog, Vargas and Savilla (1949) observed a rise in pulmonary arterial pressure. Because of the untoward effects inherent in the administration of this drug, it was decided to investigate the effect of dihydro-ergotamine (DHE) on the pressure in the pulmonary artery, in man.

(2) New evidence was sought to demonstrate the existence of pulmonary vasoconstriction in heart failure. Sodium nitrite was given, because of its well known direct chemical effect on various vessels.

(3) Finally it was decided to investigate the effect of ganglionic, sympathetic, and central nervous blocking on pulmonary hypertension in heart failure.

Methods and Material

Investigations were carried out on 43 men and women, in the early morning hours, at least eight hours after the intake of their last meal. Thirty-six of them suffered from chronic congestive heart failure. Before the observations, barbiturate was administrated in a dose of 0·10 g. by intramuscular injection.

Cardiac catheterization was performed in all the cases, in the usual manner, as described before (Halmágyi *et al.*, 1952). The tip of the catheter was placed in the right ventricle or in the pulmonary artery. Oxygen consumption was measured electrically by using a Noyons type of diapherometer (Kipp and Zonen, Delft, Holland). Arterio-venous oxygen difference was determined photo-electrically (Issekutz Jr., *et al.*, 1949). All pressure measurements were done with a Sanborn electromanometer (Rappaport and Sarnoff, 1949).

The term " pulmonary arterial pressure " indicates in this study the systolic pressure of the right ventricle or that of the pulmonary artery.

Pulmonary and peripheral arterial systolic resistances were calculated by using the following equation (Riley *et al.*, 1948) :

$$R=\frac{P\times 1332\times 60}{CI}$$

where

R=resistance in the pulmonary or systemic circuit, dyne/sec./cm.$^{-5}$/m^2 body surface area (BSA),
P=systolic pressure in the pulmonary or systemic arteries, in mm.Hg, and
CI=cardiac index, ml./min.

If not stated otherwise, substances were administered by a slow intravenous, intracardiac, or intrapulmonary injection by means of an electric pressure pump. These different ways of administration did not significantly modify their effect.

The dose of DHE (Sandoz) was 1·0 mg., and that of sodium nitrite 400–600 mg. The effect of ganglionic and sympathetic blocking on pulmonary pressure was studied by administering

tetra-ethylammonium bromide (TEAB), 2–3 mg. per kg. body weight, and *N*, *N*,-dibenzyl-β-chloroaethylamine-HCl (dibenamine), 0·5–2·0 mg. per kg. body weight, the latter with a speed of 0·05 mg. per kg. body weight per min. The role of the central nervous system in maintaining pulmonary arterial hypertension was studied during sleep. The methods, with which sleep was induced, and the criteria for optimal sleep are described in an earlier paper (Halmágyi *et al.*, 1952)

Since different causes act in establishing pulmonary hypertension in the failure of the left ventricle and mitral stenosis it was hoped that the comparison of the effect of similar substances on these two, ætiologically different, but dynamically identical, forms of pulmonary hypertension would help us to distinguish the peripheral and pulmonary causes of the changes observed.

TABLE I

THE EFFECT OF VARIOUS AGENCIES ON HEART RATE, SYSTEMIC ARTERIAL AND PULMONARY PRESSURES AND CARDIAC OUTPUT IN CHRONIC HEART FAILURE

Sign of groups	Agency investigated	Diagnosis	Number of cases	Mean heart rate			Mean systolic arterial pressure, mm. Hg			Mean systolic pulmonary arterial pressure, mm. Hg			Mean cardiac index lit/min.		
				b	*a*	*d*	*b*	*a*	*d*	*b*	*a*	*d*	*b*	*a*	*d*
A	DHE	Mostly normals	10	86	84	−2	124	128	+4	23	32	+9	4·24	4·18	−0·06
B	Sodium nitrite	Mitral stenosis	4	94	88	−6	121	115	−6	50	45	− 5	2·74	3·04	+0·30
		Left heart failure	5	91	89	−2	139	132	−7	71	58	−13	2·42	2·67	+0·25
C	TEAB	Mitral stenosis	5	73	81	+8	111	101	−10	42	31	−11	3·16	3·60	+0·44
		Left heart failure	5	88	93	+5	171	135	−36	39	31	−8	2·87	2·87	0·00
D	Diben-amine	Mitral stenosis	4	71	71	0	129	121	−8	40	29	−11	4·30	4·63	+0·33
		Left heart failure	4	91	87	−4	169	153	−16	51	40	−11	4·36	4·11	−0·25
E	Sleep	Mitral stenosis	3	91	82	−9	120	108	−12	74	53	−21	2·93	3·20	+0·27
		Left heart failure	3	88	80	−8	132	107	−25	50	32	−18	2·54	2·79	+0·25

b=before, *a*=after, and *d*=difference between the two previous values.
DHE=dihydro-ergotamine. TEAB=tetra-ethylammonium bromide.

Owing to the many groups of individual experiments, a form of tabulation was devised, allowing an easy survey of the results. Tables I and II show mean values of the individual experiments. Groups B–E were divided in two sub-groups. The sub-group " mitral stenosis " consisted of cases where clinical, X-ray, and cardiographic evidence, and in some cases digital palpation during surgical valvotomy, permitted the diagnosis of pure or predominant mitral stenosis. The sub-group of " left heart failure " consisted of patients with mitral and aortic regurgitation, hypertension, and heart failure due to coronary disease and arteriosclerosis.

Results

The detailed results are shown in Tables I and II. Only some main features are emphasized below.

The significant increase in pulmonary pressure and resistance observed following the administration of DHE (Tables I and II, Group A, Fig. 3 and 4) appeared within a few minutes and could still be demonstrated after an hour. It remained uninfluenced by TEAB, but dropped promptly to normal levels after the administration of sodium nitrite (Fig. 1).

TABLE II

The Effect of Various Agencies on Peripheral and Pulmonary Systolic Resistance in Heart Failure

Sign of groups	Agency investigated	Diagnosis	Number of cases	Peripheral systolic resistance, dyne/sec./cm.$^{-5}$/m.^{2} BSA			Total pulmonary systolic resistance, dyne/sec./cm.$^{-5}$/m.^{2} BSA		
				b	*a*	*d*	*b*	*a*	*d*
A	DHE	Mostly normals	10	2,320	2,460	+140	435	612	+177
B	Sodium nitrite	Mitral stenosis	4	3,540	3,003	−537	1,605	1,300	−305
		Left heart failure	5	4,580	3,980	−600	2,350	1,738	−612
C	TEAB	Mitral stenosis	5	3,090	2,250	−840	1,062	689	−373
		Left heart failure	5	4,780	3,420	−1,360	1,080	865	−215
D	Diben-amine	Mitral stenosis	4	2,400	2,095	−305	755	500	−255
		Left heart failure	4	3,100	2,970	−130	937	780	−157
E	Sleep	Mitral stenosis	3	3,280	2,700	−580	2,020	1,350	−670
		Left heart failure	3	4,170	3,070	−1,100	1,580	917	−663

b=before, *a*=after, *d*=difference between the two previous values.
DHE=dihydro-ergotamine. TEAB=tetra-ethylammonium bromide.

The administration of sodium nitrite was followed by a significant decrease in pulmonary pressure and resistance both in mitral stenosis and left heart failure (Tables I and II, Group B, Fig. 3 and 4). No relationship was found, however, between the decrease of systemic and pulmonary pressures (Fig. 5). The decrease in pulmonary artery pressure lasted about 30–50 minutes.

The decrease in pulmonary resistance following TEAB in mitral stenosis was significantly lower than that observed in left ventricular failure. A similar difference could be demonstrated after the administration of dibenamine (Tables I and II, Groups C and D, Fig. 3 and 4). This fact implies that the simultaneous decrease in peripheral resistance bears no relationship to the resulting pulmonary hypotension. The absence of much increase in cardiac output after TEAB may be explained by the small dose used in our experiments. The decrease in pulmonary pressure following TEAB lasted 15–25 minutes.

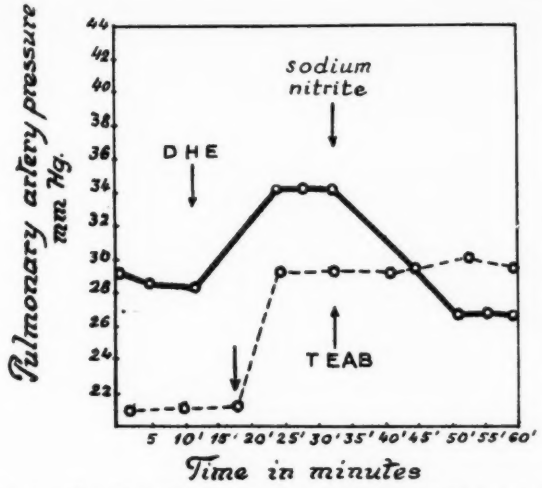


FIG. 1.—The effect of sodium nitrite and TEAB on DHE-induced pulmonary pressure elevation.

Dibenamine was effective in reducing pulmonary pressure and resistance in a dose which is generally regarded as insufficient to evoke therapeutic effects. The decrease of pulmonary pressure occurred a few minutes after the administration of the drug had been completed, before mydriasis, coryza, significant arterial hypotension (Nickerson *et al.*, 1948), or venous hypotension (Fejfar and Brod, 1951 ; Halmágyi *et al.*, 1952) had appeared.

The most significant decrease in pulmonary pressure and resistance was observed during sleep (Tables I and II, Group E, Fig. 3 and 4). Pulmonary pressure returned to pre-existing levels promptly after waking the patient (Fig. 2).

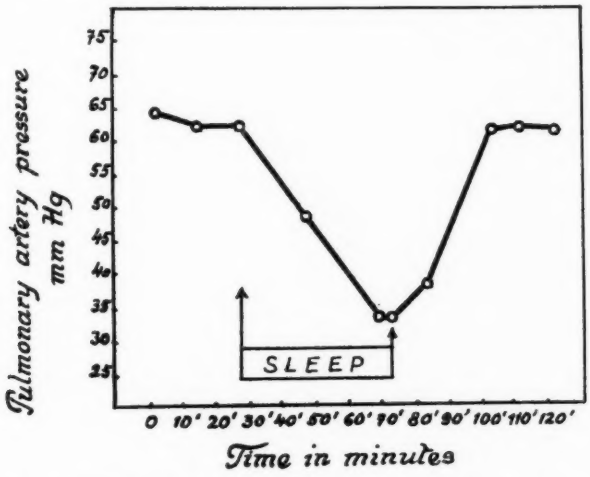
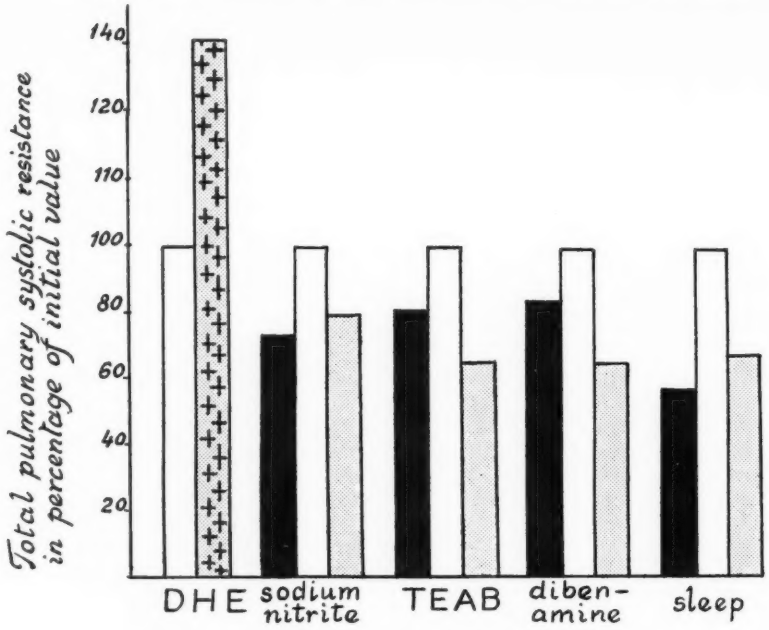


FIG. 2.—The effect of sleep on pulmonary artery pressure in chronic congestive heart failure.



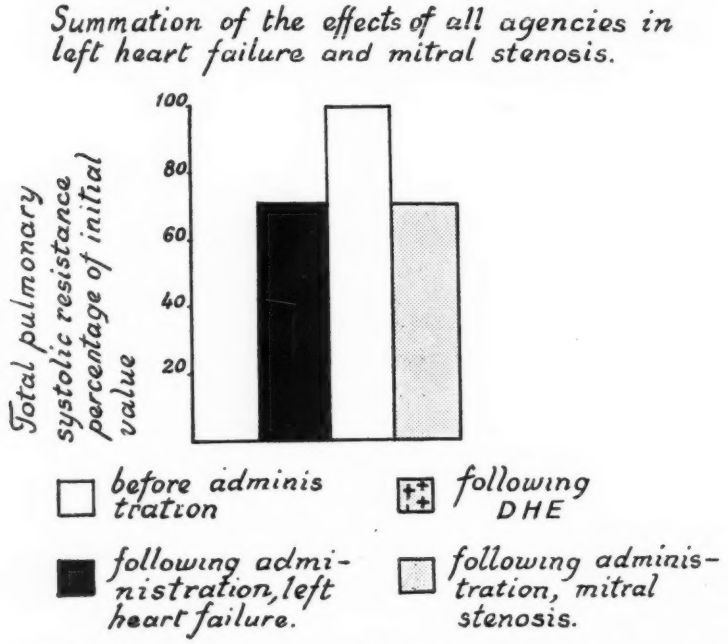


FIG. 3.—Percentage change in total pulmonary systolic resistance following various agencies.

By summarizing the effect of all these agencies on pulmonary resistance in mitral stenosis and left heart failure, it was found that the decrease was equal in both groups (Fig. 3 and 4).

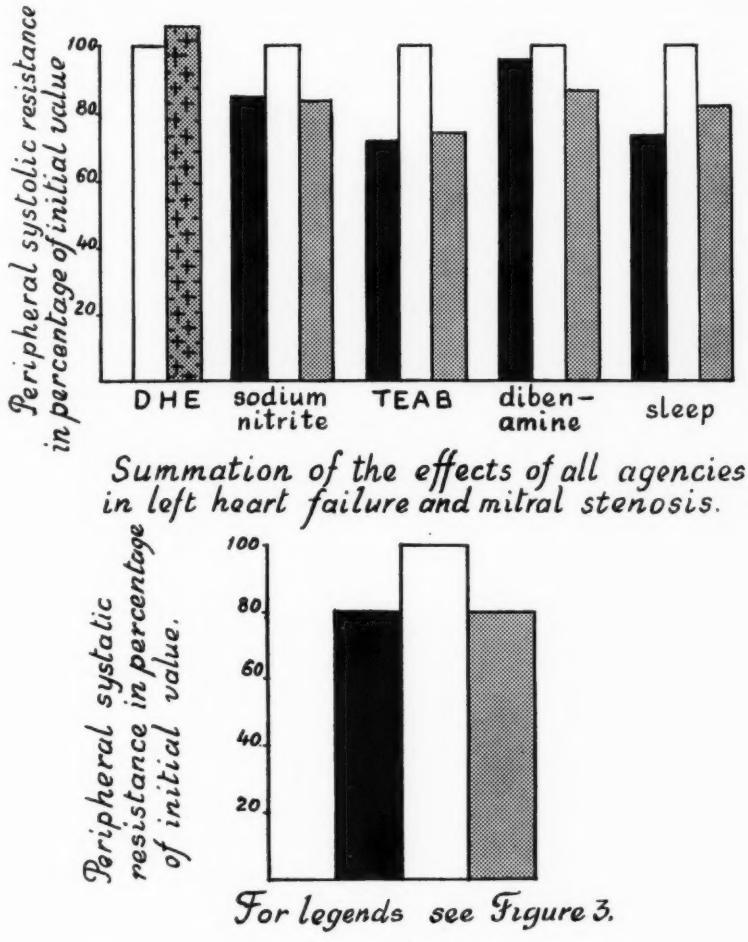


FIG. 4.—Percentage change in peripheral systolic resistance following various agencies in heart failure. Peripheral systolic resistance in percentage of initial value. For legends see Fig. 3.

DISCUSSION

DHE elevates pulmonary arterial systolic pressure and resistance without affecting the systemic circulation. This effect seems to be due to pulmonary vasoconstriction : it is completely reversed by sodium nitrite. DHE induces pulmonary vasoconstriction by a direct chemical action : TEAB neither prevents nor abolishes pulmonary hypertension following the administration of DHE.

Earlier investigators failed to observe any effect of sodium nitrite or related compounds on the pressure in the pulmonary artery (Cournand, 1947 ; Hamilton, 1951). All these former experi-

ments were carried out on normal men and animals: sodium nitrite causes a dilatation of constricted vessels only and the pulmonary vessels in normal men and animals are not constricted. The decrease in pulmonary pressure in heart failure following the administration of sodium nitrite may be regarded therefore as a good proof of the existing pulmonary vasoconstriction. The thickening of the smaller arteries in mitral stenosis (Larrabee *et al.*, 1949) and in mitral insufficiency (Becker *et al.*, 1951) is caused in part by muscular tissue. Our findings constitute, therefore, the physiological counterpart of this anatomical evidence of muscular hypertrophy of the pulmonary vessels in heart failure.

The effect of dibenamine and that of TEAB corroborates the assumption that the origin of this vasoconstriction is neurogenic, and is mediated by the sympathetic nervous system. In face of the rapid effect of small doses of dibenamine on pulmonary pressure one is inclined to suppose

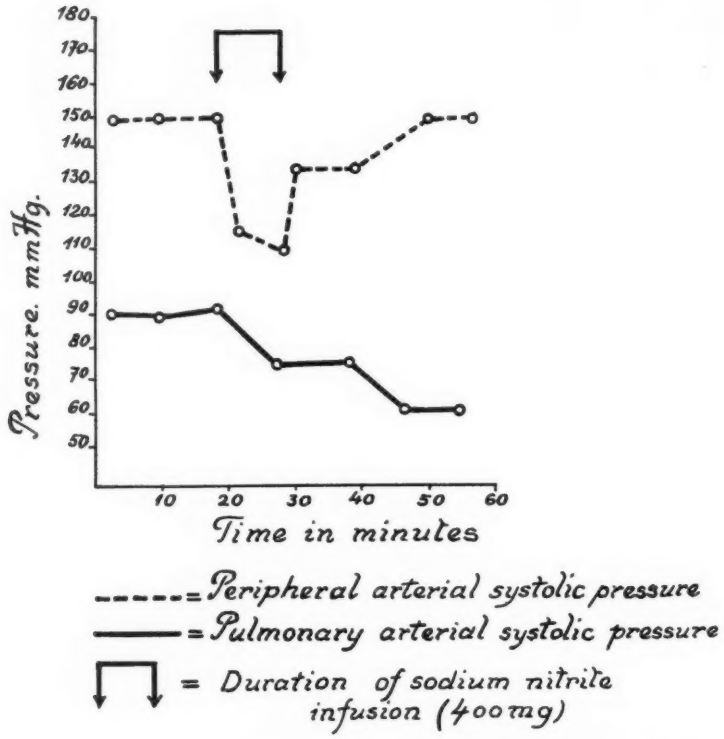


FIG. 5.—Simultaneous tracings of systemic and pulmonary arterial pressures following the administration of sodium nitrite in left heart failure.

that this phenomenon is due to a direct action on the receptor bodies of the pulmonary vessels. The decrease in pulmonary pressure during sleep strongly emphasizes the significance of the central nervous system as a possible source of that stimulus, which maintains pulmonary vasoconstriction in heart failure.

It is supposed that this vasoconstriction occurs in the arterioles of the pulmonary vascular tree.

The physiologic and clinical importance of a *static* increase in pulmonary arteriolar resistance was excellently pictured by Lewis *et al.* (1952), in regard to mitral stenosis. A *dynamic*—i.e. functional—increase is of a still major importance. Its validity extends to both kinds of heart failure, as supported by the uniformity of the effects on pulmonary hypertension of muscular and neural blocking. The sequence of events may be described as follows.

Receptor bodies in the pulmonary vessels are sensitive to an elevation of pulmonary venous pressure. A slight increase in this pressure results through the sympathetic and central nervous system in a vasoconstriction of the pulmonary arterioles, with a consequent further increase in pulmonary arterial pressure. This creates a highly effective damper to sudden surges of output by the right ventricle. The extent to which this mechanism is helpful varies from patient to patient. An " overshoot " results in an extreme elevation of pulmonary artery pressure which, by protecting the capillaries from sudden increase in pressure, further decreases cardiac output and leads to an impairment of the right ventricle. In the absence of this mechanism the pulmonary capillaries are freely exposed to the high pressure in the pulmonary arteries, since egress of blood flow from the lungs is obstructed. These are the patients who experience frequent attacks of dyspnœa and œdema of the lungs (Lewis *et al.*, 1952). This is the combination that occurs during sleep. This disturbed adaptation, promoted by the increased blood volume accompanying sleep (Menzel, 1940 ; Perera and Berliner, 1943), may be one of the many causes in the production of cardiac asthma and pulmonary œdema in heart failure.

The cause of the excitation of the central nervous system remains unsolved. Anoxia is generally thought to be a direct chemical stimulus : its effect is uninfluenced by surgical or chemical sympathectomy.

The above observations are in good accordance with Speransky's view (1950) : " The participation of the nervous system of a complex organism extends without exception to all its functions."

Summary

Administration of dihydro-ergotamine increases pulmonary arterial systolic pressure and resistance by constricting the pulmonary vessels. This pulmonary hypertension is abolished by the administration of sodium nitrite through its direct chemical effect on the pulmonary vessels. Pulmonary hypertension in heart failure also decreased after the administration of sodium nitrite. This was considered to be evidence of pulmonary vasoconstriction in heart failure. Tetra-ethyl-ammonium bromide and dibenamine, by relieving neurogenic vasoconstrictor tone, also decreased pulmonary pressure and resistance in heart failure. A similar effect was observed during sleep, and was taken as evidence of the role of the central nervous system in the pathogenesis of pulmonary hypertension in heart failure.

The significance of these findings is stressed, with special reference to the genesis of paroxysmal nocturnal dyspnœa and pulmonary œdema.

Our thanks are due to Messrs. Sandoz Ltd., Basel, Switzerland, for liberal supply of dihydro-ergotamine, and to Mr. K. Szeitz for his invaluable help and assistance.

References

Bayliss, R. I. S., Etheridge, M. J., and Hyman, A. L. (1950). *Lancet*, **2**, 889.
Becker, D. L., Burchell, H. B., and Edwards, J. E. (1951). *Circulation*, **3**, 230.
Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W. (1946). *J. clin. Inves.*, **25**, 639.
Borden, C. W., Ebert, R. W., Wilson, R. H., and Wells, H. S. (1950). *New Engl. J. Med.*, **242**, 529.
Cournand, A. (1947). *Bull. N.Y. Acad. Med.*, **23**, 27.
—— (1950) *Circulation*, **2**, 641.
Daly, I. De B., and Hebb, C. O. (1942). *Quart. J. exp. Physiol.*, **31**, 211.
——, —— (1952). *Quart. J. exp. Physiol.*, **37**, 19.
Dexter, L. (1952). *Bull. N.Y. Acad. Med.*, **28**, 90.
——, Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K. (1950). *J. clin. Invest.*, **29**, 602.

Dirken, M. N. J., and Heemstra, H. (1948). *Quart. J. exp. Physiol.*, **34,** 193 ; 213 ; 227.
Dixon, W. E., and Hoyle, J. C. (1930). *J. Physiol.*, **70,** 1.
Doyle, J. T., Wilson, J. S., and Warren, J. V. (1951). *Federation Proc.*, **10,** 37.
Fejfar, Z., and Brod, J. (1951). *Sbornik Lekar.*, **53,** 99. (In Czech.)
Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J. (1950). *J. Clin. Invest.*, **29,** 1387.
Gaylor, J. B. (1934). *Brain*, **57,** 143.
Greene, D. G., and Bunnell, I. L. (1950). *J. clin. Invest.*, **29,** 818.
Halmágyi, D., Felkai, B., Iványi, J., and Heténvi Jr., G. (1952). *Brit. Heart. J.*, **14,** 101.
Hamilton, W. F. (1951). *J. Allergy*, **22,** 397.
Hochrein, M. (1938). *Klin. Wschr.*, **17,** 438.
Issekutz Jr., B., Heténvi Jr., G., and Feuer, I. (1949). *J. Physiol.*, **108,** 32.
Kuntz, A. (1946). *The Autonomic Nervous System.* Ballière, Tyndall and Cox, London.
Larrabee, W. F., Parker, R. L., and Edwards, J. E. (1949). *Proc. Staff. Meet. Mayo Clin.*, **24,** 316.
Larsell, O., and Dow, R. S. (1933). *Amer. J. Anat.*, **52,** 125.
Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L. (1952). *Amer. Heart J.*, **43,** 2.
Liljestrand, G. (1948). *Arch. intern. Med.*, **81,** 162.
Menzel, A. (1940). *Klin. Wschr.*, **18,** 29.
Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Dresdale, D. (1947). *Amer. J. Physiol.*, **150,** 315.
Nickerson, M., and Goodman, L. S. (1948). *Federation Proc.*, **7,** 397.
Parin, V. V. (1943/44). *Amer. Rev. Soviet Med.*, **1,** 251.
Parker, Jr., F., and Weiss, S. (1936). *Amer. J. Path.*, **12,** 573.
Pearce, J. W., and Whitteridge, D. (1951). *Quart. J. exp. Physiol.*, **36,** 177.
Perera, G. A., and Berliner, R. W. (1943). *J. clin. Invest.*, **22,** 25.
Puder, S. (1938). *Tubercle*, **19,** 448.
—— (1941). *Virchow's Arch.*, **308,** 153 ; 161.
Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A. (1948). *Amer. J. Physiol.*, **152,** 372.
Rappaport, M., and Sarnoff, S. J. (1949). *Federation Proc.*, **8,** 130.
Scherff, D., and Schönbrunner, E. (1937). *Klin. Wschr.*, **16,** 340.
Schwiegk, H. (1935). *Pflüger's Arch.*, **236,** 206.
Speransky, A. D. (1950). *Grundlagen der Theorie der Medizin.* Sänger, Berlin.
Sternberg, H., and Tamari, M. (1928). *Arch. ges. exp. Path. Pharm.*, **136,** 34.
Takino, M. (1933). *Acta Scholae Med. Kyoto*, **15,** 321.
Vargas, J. J., and Savilla, V. S. (1949). *Rev. Espanol. Fisiol.*, **5,** 19.

THE EFFECT ON THE HUMAN THIRD HEART SOUND OF VARIATIONS IN THE RATE OF FILLING OF THE HEART

BY

A. W. SLOAN AND MARY WISHART

From the Institute of Physiology, University of Glasgow

Received May 29, 1952

The first descriptions of the physiological third heart sound (Gibson, 1907; Hirschfelder, 1907) related its occurrence to the presence of a wave in the venous pulse immediately following the V wave. Thayer (1908) showed that the sound occurs simultaneously with the downstroke of the V wave or the upstroke of the wave that immediately follows; this corresponds to the period in the cardiac cycle when the rate of filling of the ventricles is maximal, just after the opening of the atrio-ventricular valves. Because of its time of occurrence the third heart sound has been called the " rapid-filling " sound.

The physiological third heart sound is best heard at, or a short distance medial to, the cardiac apex, with the subject recumbent and lying on the left side. On auscultation it seems louder if the rate of venous return of blood to the heart is increased by moderate exercise (Gallavardin, 1912), by raising the patient's arms and legs (Thayer, 1909), or by pressure on the abdomen (Gibson, 1907).

Observers who attempted to record the third heart sound by phonocardiography after exercise have differed in their findings. Bridgman (1915) found an increase in the sound deflections immediately after exercise, whereas Mannheimer (1940) found a diminution.

The improved electronic techniques employed in modern phonocardiography offer an opportunity to demonstrate objectively any alterations in loudness of the heart sounds with varying rates of venous inflow of blood. Linear, stethoscopic, and logarithmic phonocardiograms may be recorded as recommended by Rappaport and Sprague (1942). The deflections on the linear records vary in size with the amplitude of the original vibrations. The deflections on the logarithmic records vary with the loudness of the original sounds as heard by the human ear.

METHOD

The subjects selected for the investigation were 16 healthy young adults, each of whom showed an obvious third heart sound on the logarithmic phonocardiogram. The group consisted of 10 men and 6 women, and their ages ranged from 16 to 24 years.

The electronic phonocardiograph employed to record the heart sounds is fully described elsewhere (Campbell, Sloan, and Andrew, 1952). The jugular phlebogram was used as the reference tracing for the phonocardiogram since the physiological third heart sound can be distinguished from other diastolic sounds by its relationship to the V wave of the phlebogram. An electrocardiogram (lead II) was also recorded from each subject to confirm the interpretation of the phlebogram.

Five recordings were taken from each subject. On each one the amplitude of deflection for each sound was measured over five cardiac cycles and the average amplitude calculated.

The first two records were preliminary controls, one with the cardiogram, and the other with the phlebogram as reference tracing; they were taken after the subject had been lying down for approximately five minutes. Sphygmomanometer cuffs were then applied to both thighs and both arms

and were inflated to the diastolic blood pressure of the individual. According to McMichael and Sharpey-Schafer (1944) interruption of the venous return from the limbs by this method produces a considerable fall in the right atrial pressure. The sphygmomanometer cuffs were rapidly inflated by connecting them through a stopcock to a reservoir of compressed air; the cuffs were maintained at diastolic blood pressure for five minutes, at the end of which time a further recording was taken. The pressure was then released and, after allowing a further five minutes for the circulation to return to normal, another control record was taken. The subject then performed a cycling movement of the legs in the air for two minutes, while remaining supine, and a final record was taken immediately on completion of this exercise.

The chest-piece of the stethoscope leading to the microphone was firmly held over the cardiac apex by a rubber band round the chest and remained in position throughout each observation. In two cases no valid record was obtained after exercise due to shifting of the chest-piece during the muscular movement. The gain of the amplifier was constant during each observation but it was of necessity altered for different subjects owing to the wide individual variation in intensity of the heart sounds. Consequently the alterations in amplitude of the phonocardiogram deflections were comparable within each individual experiment but were not comparable from subject to subject. The changes in amplitude were therefore determined in terms of percentage increase or decrease.

Results

The records obtained from one of the subjects are shown in the Figure. Venous occlusion is seen not to affect the first and second sounds but the third sound is almost abolished. Exercise results in a considerable increase in amplitude of both the first and the third sounds.

With venous occlusion the third sound deflections were either abolished or diminished in every subject. The individual changes were relatively uniform, the extreme values being −50 per cent and −100 per cent. The effect on the first and second sounds was negligible, the individual changes being small and variable.

After exercise the third sound deflections were increased in amplitude in 10 of the 14 subjects, the individual changes varying from +10 per cent to +200 per cent. Four subjects showed no alteration in the amplitude of the third sound. The first sound was increased in amplitude in every subject. The second sound showed a variable response; in the majority of cases there was a small increase. The mean reduction in amplitude of the third sound deflections with venous occlusion and the mean increases of first and third sound deflections after exercise were statistically highly significant ($P<0{\cdot}01$).

There was a negligible change in heart rate with venous occlusion of the limbs. The rate was increased with exercise in every case but one. The individual alterations in the heart rate with exercise did not correspond to the individual variations in the response of the third heart sound.

Discussion

Of the three normal heart sounds, only the third is consistently diminished by reduction in the rate of filling of the heart.

An increase in the rate of filling of the heart increases the amplitude of the vibrations of the first and third sounds but the effect on the third sound is not so consistent as that caused by reducing the venous return. This might be expected from the contradictory findings of Bridgman (1915) and Mannheimer (1940). Since there is no correlation between the rate of the heart and the amplitude of the deflections of the third heart sound, the failure of the sound to increase after exercise in some cases cannot be explained by a reduced inflow per beat due to tachycardia. It seems, therefore, that other circulatory changes associated with muscular exercise, in addition to the rate of inflow of blood to the ventricles, must influence the production of the third heart sound.

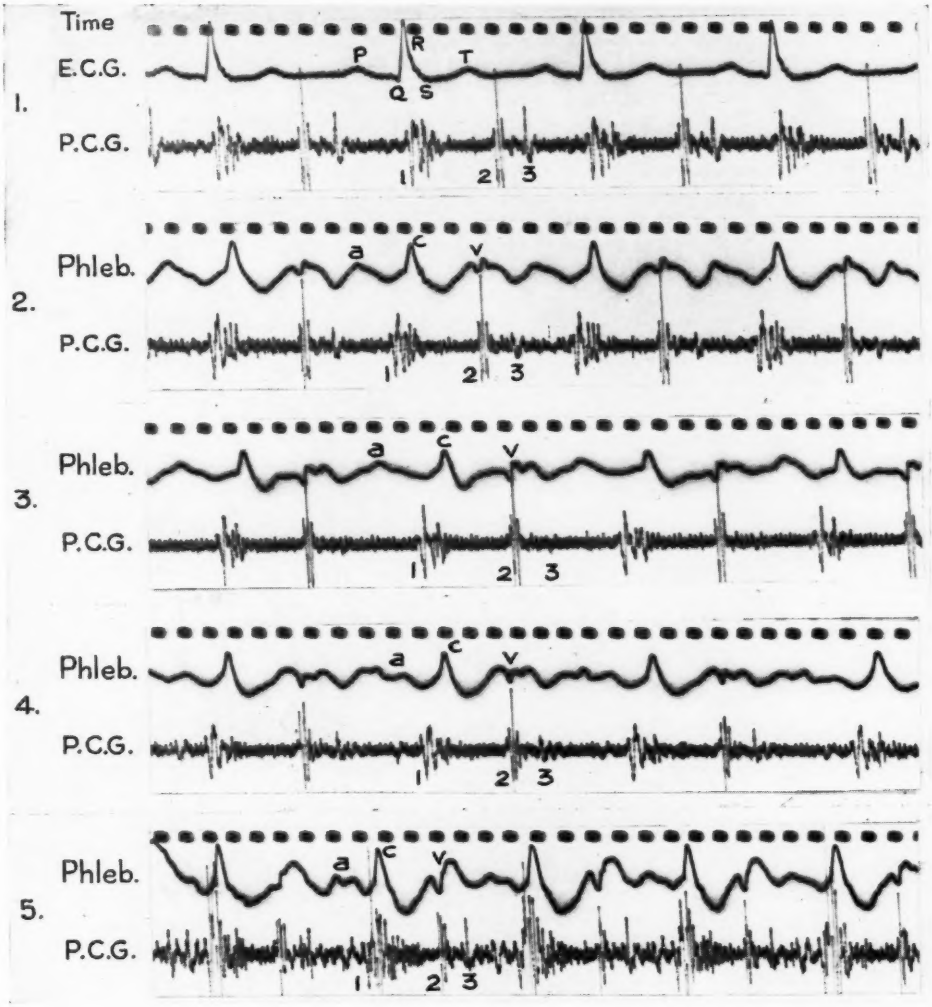


FIG.—Set of records from one subject. 1 and 2, preliminary controls; 3, with venous occlusion; 4, control after venous occlusion; 5, after exercise. E.C.G.=electrocardiogram (lead II); Phleb.=jugular phlebogram; P.C.G. =logarithmic phonocardiogram. Time marking in 1/10 sec.

The balance of evidence seems to favour the relationship of the third heart sound to the rate of filling of the heart and to justify the use of the term, " rapid-filling " sound.

SUMMARY

Logarithmic phonocardiography on 16 human subjects showed that deflections due to the third heart sound were reduced in amplitude in every case when the venous return from the limbs was obstructed.

In 10 out of 14 subjects the third sound deflections were increased in amplitude after muscular exercise: in the remaining 4 the deflections were unchanged.

Changes in the first and second sounds were less consistent.

Our thanks are due to Professor R. C. Garry for advice and criticism and to Mr. A. C. Bain for technical assistance Expenses were defrayed by a grant from the Rankin Medical Research Fund of the University of Glasgow.

References

Bridgman, E. W. (1915). *Heart*, **6**, 41.
Campbell, F. W., Sloan, A. W., and Andrew, A. M. (1952). *Brit. Heart J.*, **14**, 271.
Gallavardin, L. (1912). *Arch. Mal. Cœur*, **5**, 776.
Gibson, A. G. (1907). *Lancet*, **2**, 1380.
Hirschfelder, A. D. (1907). *Johns Hopkins Hosp. Bull.*, **18**, 265.
McMichael, J., and Sharpey-Schafer, E. P. (1944). *Brit. Heart J.*, **6**, 33.
Mannheimer, E. (1940). *Acta pædiatr., Stockh.*, **28**; Supp. 2.
Rappaport, M. B., and Sprague, H. B. (1942). *Amer. Heart J.*, **23**, 591.
Thayer, W. S. (1908). *Boston med. surg. J.*, **158**, 713.
—— (1909). *Arch. intern. Med.*, **4**, 297.

RHEUMATIC PERICARDITIS

BY

G. T. THOMAS, E. M. M. BESTERMAN, AND A. HOLLMAN

From the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, Bucks

Received August 8, 1952

Opinions on prognosis in rheumatic pericarditis have differed widely. The same may be said of other and less important aspects: its frequency (Schlesinger, 1938; Ash, 1942); the sex and age incidence (Coombs, 1924; Findlay, 1932); the interval after the onset of the rheumatic state before it develops (Gibson, 1936); and the frequency of electrocardiographic changes (Bellet, 1938; Nay, 1949; Wood, 1950). We have studied these points and have found striking differences between them in cases with dry pericarditis only and in those with effusion. In the past, little or no attempt has been made to distinguish between these two types, and this may account for many of the discrepancies in the findings. One object of this paper, therefore, is to emphasize what differences there are between dry pericarditis and pericarditis with effusion. Cases with effusion have also been studied in detail to determine any specific clinical features that they may show, to see what clinical signs occur most frequently and which of them appear early and are therefore most useful in diagnosis, and to correlate the electrocardiographic changes with alterations in size of the effusion.

A Comparison between Dry Pericarditis and Pericarditis with Effusion

Altogether there were 38 cases in the series: 30 of them had effusion, and 8 had dry pericarditis only. The sex and age incidence was somewhat different in the two. Effusion occurred with equal frequency in the two sexes and the two age groups, five–ten and eleven–fifteen years, whereas dry pericarditis was more common in boys between eleven and fifteen (Table I). These differences, however, are not statistically significant.

All 8 cases with dry pericarditis survived; 15 of the 30 with effusion died (Table I). This difference is not likely to occur by chance alone ($x^2 = 6{\cdot}6$; $P = 0{\cdot}01$), but may be explained by differences in the duration of preceding rheumatic activity in the two groups (see below).

TABLE I

The Sex and Age Incidence and Mortality in Pericarditis—with and without Effusion

Type of pericarditis	Number of cases	Sex		Age (in years)			Number of deaths
		Boys	Girls	5–10	11–15	16–20	
With effusion	30	15	15	16	13	1	15
Without effusion	8	6	2	1	6	1	0

More detailed comparison between the two types was possible in only 17 of the 30 with effusion and 7 of the 8 with dry pericarditis, for in the remainder the onset of pericarditis preceded admission to this hospital and the previous data were inadequate. In all 7 cases with dry pericarditis, pericardial friction developed during the first month of rheumatic activity, whereas 12 of the 17 effusions occurred after the end of the first month, and 3 of them after the end of the sixth month or later. The duration of preceding rheumatic activity had a direct bearing on the outcome of cases with effusion, for the 5 in which the effusion developed during the first month all survived, whereas 10 of the 12 that developed later died. Pericardial friction was heard in the " dry " cases for between two and twenty-four days, in 5 of them for four days or less. Effusion, on the other hand, persisted for two months or more in 6 of the 7 cases that survived; though in the seventh it resolved in a month. Other differences between the two groups of case were as follows. Abnormal electrocardiograms were found in 10 of the 17 with effusion, whereas the curves were invariably normal in dry pericarditis. Pain was more common in effusion that in dry pericarditis, being present in 13 with effusion and in only 2 with dry pericarditis. Tachypnœa, with rates from 40 to 70 a minute, occurred in all cases with effusion, but was never observed with dry pericarditis. The white count ranged between 13,000 and 30,000 in all but one case with effusion, and was below 13,000 in 6 of the 7 with dry pericarditis. Residual heart lesions were present in 6 of 7 cases with effusion that survived and in only 4 of the 7 with dry pericarditis.

These differences between cases with dry pericarditis only and those with effusion may well account for many of the discrepancies in the findings of previous series, for in none of them have the two types of case been differentiated. Thus Schlesinger (1938) found a mortality rate of 33 per cent and Ash (1942) of 60 per cent. In our own series there was no mortality rate for dry pericarditis; for effusion it was 50 per cent. Gibson (1936) stated that most cases occurred within two weeks of the onset of the rheumatic state. All our cases of dry pericarditis occurred during the first month: 12 of the 17 with effusion developed later. Findlay (1932) and Ash both found that a small proportion of their cases recovered without residual valve lesion—2·9 and 2·5 per cent respectively. Only 1 of our 7 effusions that survived had no residual lesion, whereas 3 of the 7 with dry pericarditis had normal hearts on discharge. Nay (1949) reported abnormal electrocardiograms in all his cases; Wood (1950) in only a quarter. All our cases with dry pericarditis had normal curves: 10 of the 17 effusions had abnormal curves.

Dry pericarditis appeared to be relatively benign: it invariably occurred during the first month of rheumatic activity, caused no electrocardiographic changes, was of short duration, and had no effect on prognosis. Effusion, on the other hand, occurred at any time during the course of the disease, frequently caused cardiographic changes, persisted for several weeks, and usually affected the prognosis adversely.

Seventeen Cases with Effusion

The clinical and electrocardiographic findings, the results of therapy, and the prognosis in 17 cases with effusion will now be described in detail.

The temperature at the onset of the effusion ranged between 101° and 104° F. Tachypnœa was invariable; it could not be accounted for by the size of the effusion, the size of any accompanying pleural effusion or by the presence of pain. In 7 cases it preceded clinical and radiographic signs of effusion, and in 3 it persisted until the effusion had diminished in size or had disappeared. Thirteen cases had pain; 11 of them for one day only, the other 2 for seven days. In the majority the pain was described as a substernal ache, aggravated by respiration and movement. The remainder had pain in the left shoulder and/or the left chest on breathing. The sedimentation rate was raised in all cases, in half of them to over 100 mm/hour (Westergren). The white blood count was raised as described.

A Correlation of the Clinical and Radiological Signs. In 15 of the 17 cases skiagrams had been taken at intervals of not more than a week throughout the course of the effusion and it was possible to correlate

the clinical with the radiological signs (Table II). In four cases abnormal physical signs were present before there was any certain X-ray evidence of effusion: 3 of them had a raised venous pressure and 3 had abnormal signs in the lung bases. At a time when skiagrams first showed effusion the most frequent abnormal findings were signs at the lung bases (14 cases), raised venous pressure (13 cases) and increased cardiac dullness (10 cases). Enlargement of the liver was present in only 4 cases but developed later in

TABLE II

CLINICAL SIGNS IN 15 CASES OF RHEUMATIC PERICARDIAL EFFUSION

Signs	Number of cases showing each of the various signs		Number of cases developing various physical signs later	Number of cases that ultimately showed each of the various signs
	When no certain X-ray evidence of effusion	When X-rays first showed effusion		
Raised venous pressure	3	13	2	15
Abnormal signs at lung bases	3	14	0	14
Abnormal cardiac dullness	1	10	2	12
Pericardial friction	1	9	2	11
Enlargement of the liver	1	4	4	8
Diminished heart sounds	0	4	0	4
Diminished apex beat	0	4	0	4

another 4. The frequency with which the various physical signs were ultimately found is shown in the last column of the table.

It is concluded that the most frequent signs of rheumatic pericardial effusion are raised venous pressure, signs at the lung bases, and abnormal cardiac dullness. The first two of these are early signs and may precede X-ray evidence of effusion. Liver enlargement is a less common sign and frequently a late one. Diminished intensity of heart sounds and disappearance of the apex beat are noticeable in only a minority of cases.

Regression of Physical Signs. Seven cases died. In the remaining 8 the regression of physical signs was observed as the skiagrams returned to normal. Signs to disappear early were raised venous pressure, pericardial friction, signs at the right base, diminished heart sounds, disappearance of the apex beat, and dullness beyond the apex beat: dullness in the second left space tended to persist, as did enlargement of the liver. In 6 cases the last abnormal findings were signs at the left base.

Though there was on the whole good correlation between regression of clinical signs and return of the skiagrams to normal, there were certain discrepancies. In 4 cases abnormal signs at the bases, and in one abnormal cardiac dullness persisted after the skiagrams had become normal. In another, all clinical signs had disappeared and yet the skiagram still showed a small effusion.

Signs at the Lung Bases. Signs at the lung bases were present in 14 out of the 15 cases; they preceded X-ray evidence of effusion in 3 and persisted after the skiagrams had returned to normal in 4. They will be considered, therefore, in detail.

All 14 cases had signs at the left base and 13 had signs at the right as well. Of those with bilateral signs, 6 developed them first in the left side, and 2 in the right; in the other 5 both sides became implicated simultaneously. The signs at the left base were invariably more extensive than those at the right and always suggested the presence of fluid; pleural rubs were heard in 3 cases. The signs at the right base were similar to those at the left in 6; in the remainder there was only dullness to percussion. Pleural rubs were heard in 3 cases.

The presence of fluid at the left base was confirmed by X-rays in all cases, and by paracentesis in three. In 12 of the 13 cases with signs at the right base there was also radiographic evidence of effusion, but to a lesser degree than on the left side. In all cases the physical signs were more obvious than the X-ray changes, and in many the presence of fluid could be demonstrated only by films taken in the oblique positions. Collapse of a lower lobe was not observed: if it occurred, it was obscured by the presence of fluid.

It is concluded that signs at the lung bases are due usually to accompanying pleural effusions: collapse

of a lower lobe is uncommon and, it is believed, occurs only under special circumstances such as secondarily to a large pleural effusion or to a purulent bronchitis, as in two recent cases. The suggestion made by Poynton (1921), that basal signs are due to compression collapse, could not be confirmed.

Electrocardiographic Findings. Electrocardiograms had been taken at weekly intervals in all but 2 of the 17 cases; in 10 they were abnormal, in 6 they were normal, and in 1 the changes were of doubtful significance.

Ten cases with Abnormal Cardiograms. The time of onset of the cardiographic changes were as follows: in 1 case S–T elevation was the first evidence of pericarditis; in 3 the curves became abnormal as clinical and X-ray signs of effusion appeared; in 5 they did not become abnormal until three to eight days after a diagnosis of effusion had been made by other means. In the remaining case the cardiogram was already abnormal and accompanied clinical and X-ray evidence of effusion when the patient was admitted.

The most frequent initial cardiographic change was S–T elevation, which was present in 6 cases: it was seen in leads I, II, VL and V6 in three of them, in leads II and VL in two, and in lead III only in one. The segment was saddle-shaped in three cases, normal in two, and coved in one. The next most frequent was a low T wave in all leads; this was present in three cases. The least frequent was T wave inversion, which was found in only one case in leads II and III.

The subsequent behaviour of the cardiogram showed considerable variation in the 10 cases, particularly when considered in relation to changes in size of the effusion: in 2 cases the curves returned to normal as the effusion increased (Fig. 1); in 2 they became normal, the size of the effusion remaining unchanged; in 6 they underwent changes over periods of two to six weeks as the effusion first increased and then diminished.

The two cases in which the curves returned to normal as the effusion increased in size showed S–T elevation for three and five days only. One died when the effusion was at its height; the curve on the day of death was normal. The other survived, and the curve remained normal apart from T wave inversion in V5 on one occasion.

Of the two cases in which the curves became normal without any change in size of the effusion, one had S–T elevation for three days, the other low T waves for fourteen days. Both died: in one of them normal curves had been found on four occasions during the month preceding death; the diagnosis were confirmed at autopsy.

Three of the six cases with more persistent cardiographic changes had initial S–T elevation. In only one did the segment remain elevated as the effusion increased in size (Fig. 2); in the other two the S–T elevation disappeared and the T waves became low (Fig. 3). Two cases had initial low T waves. In one the T waves became flattened as the effusion increased; in the other the T wave in V5 became inverted. The sixth case had normal cardiograms until the effusion was maximal; there was then T wave inversion in leads II and III. In all six cases the curves returned to normal over periods of two to six weeks as the effusions diminished in size. All showed low T waves during this time; in two of them only there was late, transitory T wave inversion in leads I and V5 respectively.

Six cases with Normal Cardiograms. In 6 cases the curves were normal. Four had had digitalis which might have masked the changes from pericarditis. The remaining two had not had digitalis, but in one of them only one cardiogram had been taken, and in the other, they had been done at only monthly intervals. Abnormalities may well have been missed, for as it has been shown, the changes may be both delayed in the time of their appearance and of only short duration.

It is concluded that abnormal electrocardiograms will be found in rheumatic pericardial effusion, provided records are taken at intervals of not less than one week from the time of onset of the pericarditis and that the patients are not taking digitalis.

Results of Therapy

Eight patients were treated with salicylates. Three of them died within three weeks of starting treatment. Of the five that survived, the clinical and radiological signs of effusion increased during therapy in two; in another two the signs of effusion were much less after ten days, but similar improvement was seen in an untreated case. The fifth showed a reduction in the size of the effusion after four days. Such rapid improvement was not observed in untreated cases, and it is possible that salicylates may have had some beneficial effect.

The pericardial sac was aspirated in one case only, a boy of twelve with a massive effusion; 15 and 20 oz.

of blood-stained fluid were removed on two occasions, but only a temporary fall in the respiration rate resulted, and death occurred a few days later.

In one case with marked dyspnœa and a large left-sided pleural effusion a pint of fluid was aspirated from the pleural cavity and considerable relief was obtained.

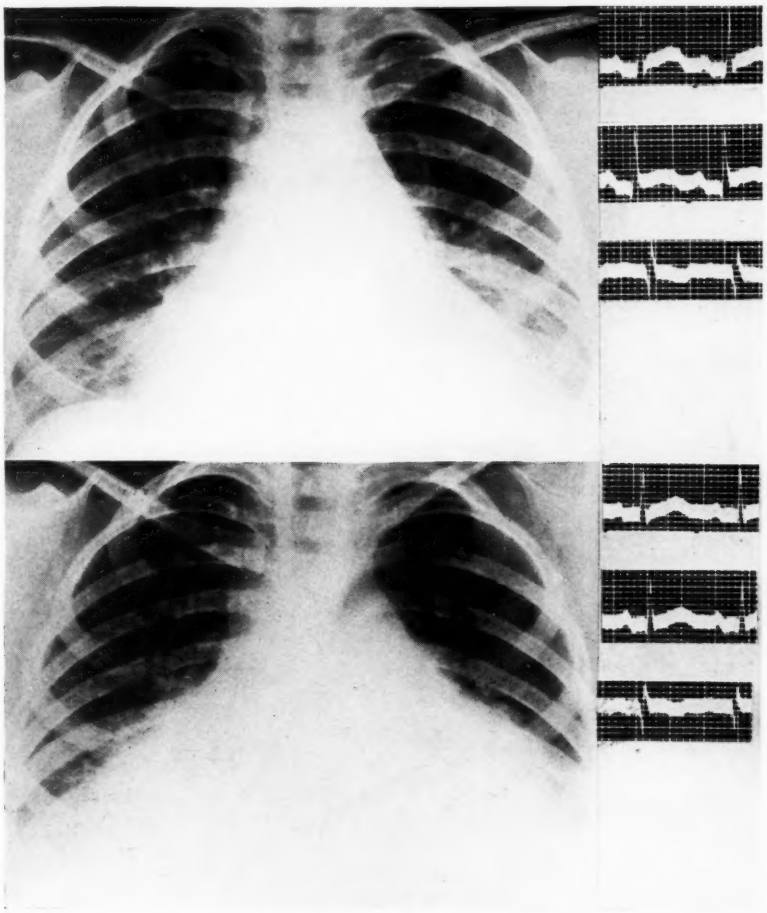


FIG. 1.—Skiagrams and standard limb leads at a week's interval to show return of electrocardiogram to normal as effusion increases in size.

PROGNOSIS

Ten out of 17 cases died. Eight of them were between the ages of five and ten, and all had had persistent rheumatic activity for many weeks or months prior to the onset of effusion. Of the 7 that survived, only one was under ten, and five had developed effusion during the first month of rheumatic activity. Thus the prognosis was worse in patients under ten years of age and after long-continued rheumatic activity.

All but one of the 7 cases that survived had residual heart lesions. In two, both mitral and aortic

incompetence were already present on admission. Of the other 4, one of whom had aortic incompetence on admission, all developed signs of mitral incompetence and one those of aortic incompetence as well. Significant murmurs did not appear in two of them until the effusion had been present for some time. In the remaining case pericardial effusion was not accompanied by other evidence of carditis; at no time were significant murmurs heard, and the heart appeared to be normal one year later.

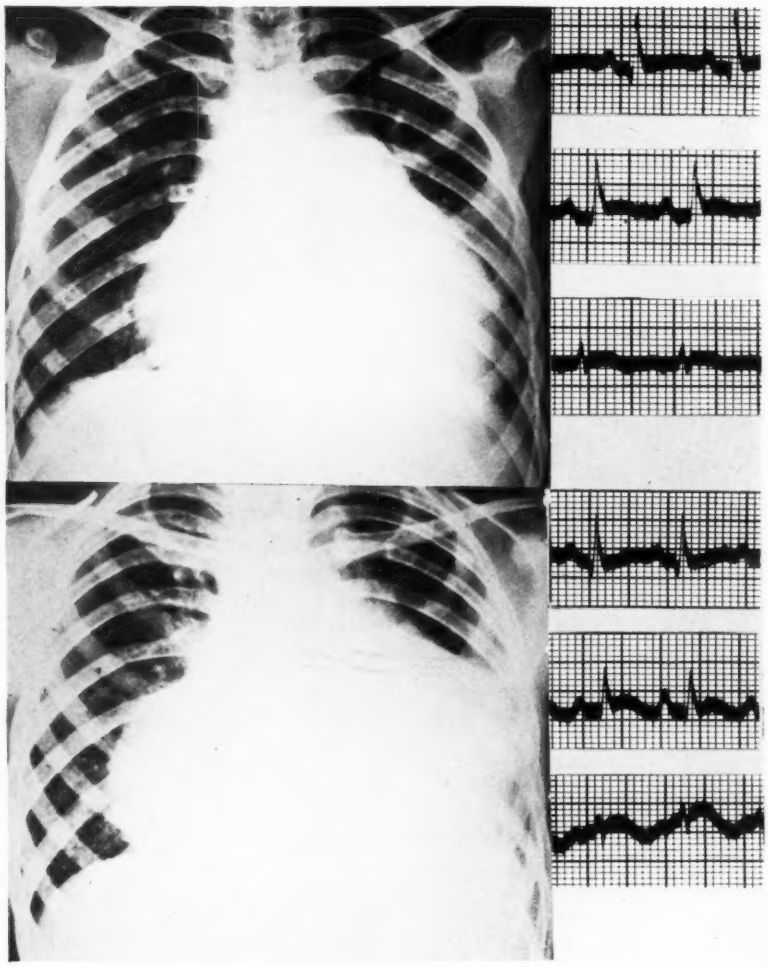


FIG. 2.—Persistent S–T elevation as effusion increases in size.

SUMMARY AND CONCLUSIONS

Thirty-eight cases of rheumatic pericarditis have been studied, 30 of them with effusion and 8 with dry pericarditis only. The importance of distinguishing between these groups has been emphasized: dry pericarditis is a relatively unimportant feature of early carditis; effusion is a

manifestation of severe carditis, occurring at any time during the course of the illness and affecting the prognosis adversely.

The clinical findings have been correlated with the X-ray changes in 15 cases with effusion.

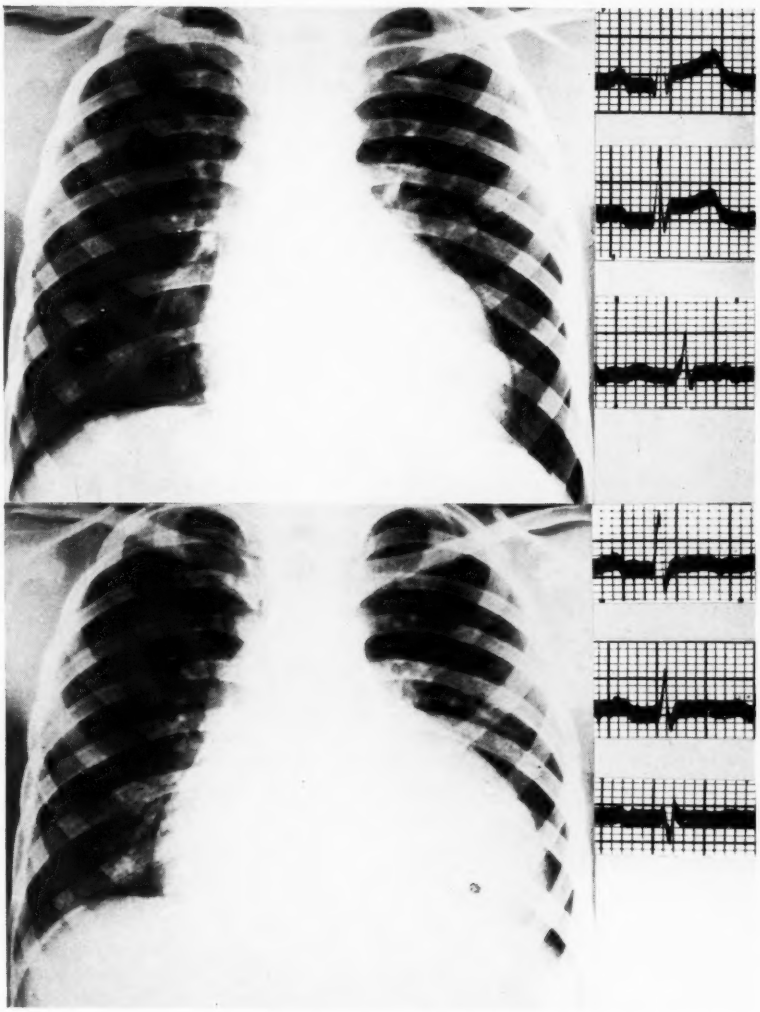


FIG. 3.—Return of S–T segment to normal and development of low or inverted T waves as effusion increases.

Raised venous pressure, signs at the lung bases, and abnormal cardiac dullness were the most common signs, the first two being early and tending to precede X-ray evidence of effusion. Signs at the lung bases could invariably be accounted for by accompanying pleural effusion.

Abnormal electrocardiograms were found in 10 of 17 cases with effusion. Changes were late in five of them, and of only short duration in four. Elevation of the S–T segment was the most

common abnormality. Conspicuous inversion of the T wave was rare. Four out of six cases with normal curves had had digitalis, and this may have obscured the characteristic pattern of pericarditis. In the remaining two cardiograms had been taken at relatively infrequent intervals, and abnormalities may have been missed.

Eight cases with effusion were treated with salicylates, only one of them with possible benefit. Pleural and pericardial paracentesis were indicated and undertaken in one case each.

The prognosis in cases with effusion was worst in children under the age of ten and when there had been long-continued rheumatic activity. Ten out of 17 cases died. Of those that recovered, all but one had signs of residual heart damage: four had mitral and aortic lesions; two had mitral incompetence. The remaining case had no abnormal physical signs at the time of discharge from hospital or at follow-up examination one year later.

We are indebted to Dr. E. G. L. Bywaters and to Dr. Paul Wood for much helpful criticism and advice.

REFERENCES

Ash, R. (1942). *Amer. J. Dis. Child.*, **63**, 1.
Bellet, S., and McMillan, T. M. (1938). *Arch. intern. Med.*, **61**, 381.
Coombs, F. (1924). *Rheumatic Heart Disease.* John Wright & Sons, Bristol.
Findlay, L. (1931). *Rheumatic Infections in Childhood.* Arnold, New York.
Gibson, S., and Denenholz, E. J. (1936). *J. Pediat.*, **9**, 505.
Nay, R. M. (1949). *J. Indiana med. Ass.*, **42**, 222.
Poynton, F. J. (1921). *Brit. med. J.*, **2**, 583.
Schlesinger, B. (1938). *Lancet*, **1**, 593.
Wood, P. (1950). *Diseases of the Heart and Circulation.* Eyre & Spottiswoode, London.

BIOPSY OF THE LEFT AURICLE IN MITRAL STENOSIS

BY

J. B. ENTICKNAP

From the Department of Pathology, Guy's Hospital

Received August 14, 1952

During the past three years operations upon the hearts of patients with mitral stenosis have been performed in increasing numbers (Baker *et al.*, 1952). An opportunity has thus arisen to study by biopsy the changes in the heart and lungs at a time when, although the disease is fully established, the patient is still in a fairly good state of health. Previous morbid anatomical studies having been performed on post-mortem material, it has always been uncertain how much of the changes seen could be ascribed to the processes of death and, to a lesser extent, to autolysis. Furthermore, although many extensive investigations of cardiac histology have been made, very little attention has been paid to the tip of the left atrium. This paper deals with the changes found in this situation and a subsequent publication will describe those found in the lingular segment of the left lung. At least one other article has appeared purporting to show that histological evidence of rheumatic activity is commonly seen in auricular biopsies ((Kuschner *et al.*, 1952) who report Aschoff bodies in 4 cases out of 11) and similar opinions have been expressed by other pathologists during public discussions. It is proposed to examine the validity of these statements in the light of the findings in a large series of patients.

Material and Methods

The main observations have been made on 71 specimens of cardiac muscle removed by Mr. R. C. Brock during the course of operations for mitral valvotomy. An incision is made into the tip of the left auricle (auricular appendage) at the beginning of this operation and through it the gloved finger is inserted. The duration of the manipulations varies from 10 to 30 minutes, during which time ether is the main anæsthetic agent, and at their conclusion the piece of tissue surrounding the wound is excised and fixed in neutral formol saline. No specimens were received from 16 of the cases of the Guy's Hospital operation series but this is not thought to have caused significant selection. All those received so far have been included in this survey.

Control material has been obtained from three sources. Human myocardium attached to fragments of fibrous tissue from 3 cases of congenital pulmonary stenosis which had been removed under similar conditions is the only material that is strictly comparable. Human auricles were obtained post mortem from a number of cases of rheumatic heart disease including four fatalities during the first week after operation and one after two months: also from 12 subjects with no evidence or history of heart disease and from 3 with benign essential hypertension, who had died from causes other than heart failure. Experimental animals were the third source, anatomically comparable specimens being obtained from 7 dogs, 5 rabbits, and 12 guinea-pigs. The dogs and half of the guinea-pigs were killed while under a similar anæsthetic to that used during the surgical operation and the rabbits and the remaining guinea-pigs by fracture of their cervical spines.

Histological methods. The tissue was embedded in paraffin wax so that, in the majority of instances, the resulting section showed the complete circumference of the auricle. In a few of them it was so arranged that the cut ends of the surgical incision were available for inspection. One section from each case was stained with Mayer's hemalum and eosin and where necessary Lendrum's modification of Mallory's trichrome method (Lendrum, 1949), Weigert's elastic tissue method, Perls's reaction for iron, Mallory's phosphotungstic acid hematoxylin, Van Gieson's stain and Gordon and Sweet's method for reticulin (1936)

were used. Serial sections extending through about 1 mm. of tissue were cut in all cases in which the appearances in the first section examined in any way resembled those of acute rheumatism and in those in which organizing thrombi were present. A few frozen sections stained with oil red revealed no excess of fat.

Results

These are set out in Tables I and II from which it can be seen that, in addition to " probable " and " possible " rheumatic lesions, a number of non-specific changes was present. Before describing these abnormalities it is necessary to define some of the terms used.

Cellular foci were said to be present when one or more localized collections of not less than five chronic inflammatory cells were seen in the interstitial tissue in any section. In Table I foci containing Aschoff cells have been recorded separately (see below).

Cubing of the endothelium is a term used to describe swelling of a sheet of surface cells so that they come to resemble columnar epithelium rather than the flat cells normally found on serous membranes.

Acute myocarditis was diagnosed when an inflammatory exudate consisting largely of polymorphonuclear neutrophil cells was present in the interstices of the myocardium.

Œdema of the myocardium implies separation of the muscle cells by clear spaces that presumably contained fluid *in vivo* and is distinct from the intra-cellullar vacuolation implied by the term next defined.

Cytoplasmic irregularity is a term used for a condition practically confined to and almost uniformly present in biopsy specimens. In sections stained with eosin the cytoplasm of the muscle cells shows all variations from a foamy vacuolated appearance that is almost unstained to an intensely coloured even cherry red or deep pink such as is commonly seen in post-mortem sections of ventricular myocardium. The appearances are even more striking if Lendrum's stain is used, when the different components of this composite stain may appear in the cytoplasm in almost any combination.

Abnormal nuclear forms. Giant nuclei are darkly stained and may be swollen up to as much as 50μ in diameter. The *bizarre forms* are even darker and have an irregular crinkled outline with a plicated appearance that suggests that they have been formed from collapse and shrinkage of the giant forms.

Rheumatic lesions have been diagnosed, for the purposes of this discussion, whenever Aschoff cells were found. The comprehensive review by Gross and Ehrlich (1934) of the appearances shown by Aschoff bodies in human hearts provides the most suitable standard of reference and the definitions there given have been accepted. They state that the Aschoff cell is large and has a variable amount of amphophilic or basophilic cytoplasm with ragged edges. Commonly the single oval nucleus shows irregular aggregations of chromatin and a dense nuclear membrane that is often folded upon itself, this being the fibrocytoid type of nucleus. In others one of the chromatin masses is stellate and larger than the rest, giving the appearance of the owl-eyed type. Either form of nucleus may become pycnotic. When these cells were arranged in groups close to which there was some fragmentation of collagen giving an appearance fairly closely resembling an Aschoff body, usually of the mosaic type, a " probable " rheumatic lesion was diagnosed. In those cases in which the cells were diffusely scattered throughout the interstitial tissue in no particular relation to one another or to collagenous changes the diagnosis of a " possible " rheumatic lesion was made.

Intimal thickenings were described as cellular when they showed the presence of lymphocytes, newly formed capillaries or large numbers of fibrocyte nuclei and as acellular when the increase of intimal bulk was due solely to homogeneous hyaline material.

Changes in the Pericardium

Irregularity of the surface due to amorphous particles, fibrin flakes, and red cells was common and a few hæmorrhages were seen; these probably resulted from operative trauma. Most of the other findings were seen with about the same frequency in the biopsy and necropsy sections but the cubing of the endothelium and the appearance of arteriolitis in a coronary vessel require further comment. The former change was much commoner in the post-mortem sections from non-rheumatic subjects and does not therefore appear to be related to this form of heart disease. The latter occurred in a patient who had no clinical indications of active disease and whose subsequent course has been in no way eventful. The lingular biopsy was substantially normal and the only other finding in the auricle was some round-celled infiltration around the vessels and elsewhere in the pericardial fat. It must therefore remain an unexplained curiosity. No Aschoff cells were seen in the pericardium in any of the sections.

Changes in the Myocardium (Table I)

It may at once be emphasized that no " probable " rheumatic lesions were found in this situation in any of the specimens, although a few separate Aschoff cells were seen in one case and small lymphocytic foci in five others. Acute myocarditis was seen once and its significance is as obscure as that of the arteriolitis found in the pericardium. The relative absence of fibrosis is also rather remarkable. *Generalized cytoplasmic and nuclear changes* were present in most of the biopsy specimens. In two cases nuclear changes were seen in the presence of homogeneous cytoplasm and in another the nuclei were entirely regular in appearance while the cytoplasm showed great irregularity. Identical cytoplasmic and nuclear appearances were seen in one of the three fragments of

TABLE I

Changes in the Left Atrial Biopsies from Patients with Mitral Stenosis

Lesion seen	Biopsies			Necropsy controls		
	Those with Aschoff cells	Those without Aschoff cells	All Biopsies	Normal	With Hypertension	All Controls
Number of cases	29	42	71	12	3	15
In pericardium:						
Cellular foci	9	12	21	3	2	5
Cubing of endothelium	7	5	12	10	3	13
Fibrosis	1	1	2	3	1	4
Adherent thrombus	1	0	1	0	0	0
Arteriolitis	0	1	1	0	0	0
Hæmorrhage	2	0	2	0	0	0
In myocardium:						
Cellular foci	2	3	5	0	0	0
Acute myocarditis	0	1	1	0	0	0
Aschoff cells	1	—	1	0	0	0
Œdema	1	1	2	0	0	0
Fibrosis	3	1	4	3	1	4
Hæmorrhage	0	1	1	0	0	0
In endocardium:						
Cellular foci	4	4	8	0	0	0
Cubing of endothelium	0	4	4	3	0	3
Rheumatic lesions—						
probable	12	—	12	0	0	0
possible	17	—	17	0	0	0
Intimal thickening—						
Thickness $>150\mu$	10	14	24	1	0	1
Diffuse—cellular	4	4	8	0	0	0
acellular	3	9	12	1	0	1
Nodular	4	12	16	0	0	0
Calcified	0	1	1	0	0	0
Containing hæmosiderin	1	2	3	0	0	0
Containing muscle	0	2	2	1	0	1

myocardium from patients with congenital heart disease. Staining with oil red showed that the cytoplasmic changes were not due to the presence of intra-cellular fat. Sections passing through the incised edge of the auricular wound showed that in this region the myocardial cytoplasm invariably had the homogeneous appearance customarily seen in post-mortem material. The necropsy specimens examined as controls to this series, with one exception, showed it, and there was no difference between those with rheumatic carditis, including one examined within four hours of death, and those without. Although the appearances of animal specimens are never identical with those of human tissues, comparable appearances were seen in one dog killed with ether from which the

auricles were removed twenty minutes post mortem and in a single guinea-pig killed by this method, as well as in one that was bled to death. Similar results were found for the occurrence of abnormal nuclear forms.

Changes in the Endocardium and Lumen

The most important changes were seen in these sites and they fall into three groups. The first two, intimal thickening and the presence of organizing thrombi, are in all probability interrelated, and the third group—lesions, the appearance of which suggests the presence of active acute rheumatism—is that to which most interest is attached.

Intimal thickening was seen in both nodular and diffuse forms. In order more precisely to evaluate the generalized form of thickening measurements of intimal thickness were made on all specimens examined and a normal range established. Four measurements were made at right angles to each other of the distance from the lumen to the border of the underlying muscle, except in those few cases in which the embedding process had caused an artificial separation, when the thickness of the separated intima was measured. In addition to this precaution, measurement of nodular thickenings and of portions of intima containing inflammatory exudate was avoided. The normal mean thickness so established was 80μ (Table II) with a standard deviation of $\pm 35\mu$,

TABLE II

The Relationship between the Presence of Aschoff Cells in the Endocardium and of Organizing Thrombi in the Auricle

	Auricles containing thrombi	Auricles not containing thrombi	Total
Probable Rheumatic lesions present ..	4	8	12
Possible Rheumatic lesions present	6	11	17
No evidence of Rheumatic activity	21	21	42

giving an upper limit of normal ($p = 0{\cdot}05$) of 150μ. In about one-third of the biopsy specimens (32%) the endocardium was thicker than this, but the proportion of thrombi or Aschoff cells was no greater in the sections from these cases than in those from the other two-thirds, nor was a history of auricular fibrillation any commoner in them. In three cases a positive Perl's reaction proclaimed the presence of blood at some stage in the development of the thickenings and in another some focal calcification had taken place. In general the nodular thickenings were entirely composed of elastic tissue while the diffuse thickenings showed variable proportions of loosely arranged and compact parallel collagen bundles with some elastic fibres. In two cases the presence of muscle cells in the thickened endocardium was rather surprising.

An interesting incidental discovery was that the endocardium of the left auricle was approximately four times as thick as that of the right (mean 22μ, range 5–59μ). The thickened endocardia of mitral stenosis subjects examined post mortem showed the same ratio.

Organizing thrombi were present in nearly half the cases (43%) but there is no significant difference in the mean endocardial thickness of the cases with and those without them (Table II). It is not, however, possible to say that these cases are the only ones that have ever had thrombi within their auricles and, indeed, it is rather unlikely that this is so. All stages of organization were seen so that in several cases it was difficult to decide whether to classify the appearances as organizing

thrombi or as endothelial thickenings. The presence of hæmosiderin has usually decided the issue in favour of a thrombus but in two cases this pigment was present in a typical acellular thickening. Further, it has been possible in several cases to show by serial section that typical cellular thickenings were directly continuous with an area of organizing thrombus (Fig. 1). In others endothelialization of plaque-like clot has been seen taking place over quite a large area.

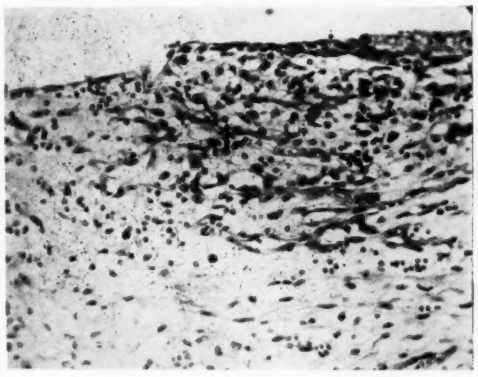


FIG. 1.—Cellular intimal thickening in continuity with organizing thrombus over which endothelium is growing. All preparations were stained with hematoxylin and eosin and were photographed at a standard magnification of × 205. The prints have been mounted parallel to the line of the endothelium.

Lesions suggestive of active acute rheumatism. In 4 cases cubing of the endothelium was seen, but here, as in the pericardium, this was commoner in the necropsy specimens and so is probably of no specific significance. Cellular foci consisting mainly of lymphocytes, although in a few cases plasma cells were seen, were present in 8 biopsy cases but not in any of the controls. Both "*probable*" and "*possible*" *rheumatic lesions* occurred with about the same frequency (12 and 17 cases respectively) (Fig. 2 and 3), and were rather commoner in those auricles that did not contain organizing thrombi (Table II). Fragmentation of collagen was present in some of these lesions but it resulted from simple loss of continuity of fibrils and was unassociated with the deep red amorphous appearance characteristic of fibrinoid when stained by eosin. Lendrum's stain did occasionally show replacement of the blue colour of healthy collagen by the yellow of the picric acid component but silver impregnation failed to reveal any argyrophil fibrils. It may then be emphasized that in no case was typical fibrinoid change of collagen seen.

Association of histological findings with evidence of sub-clinical acute rheumatism. As none of these patients had any clinical evidence of acute rheumatism at the time of operation an attempt has been made to estimate sub-clinical activity by an assessment of pre-operative temperature, erythrocyte sedimentation rate, and electrocardiogram. An unexplained temperature of over 99° F., an E.S.R. (Westergren) of above 5 mm. per hour in men and 10 mm. per hour in women, or an electrocardiographic abnormality of which the commonest was temporary post-operative fibrillation, were each given one mark. The average score for each of three groups of patients was calculated: those with nodular "probable" lesions, those with "possible" lesions and those in whom no Aschoff cells were found. The results were 1 mark for the first group, 0·5 marks for the second group, and 0·8 marks, intermediate between the other two, for the third group.

DISCUSSION

This investigation of the abnormalities seen in auricles removed from patients with mitral stenosis in whom there was no clinical evidence of either rheumatic carditis or cardiac failure has a two-fold purpose. The first is to throw some light on the thickening of the intima that is so commonly seen in healed rheumatic carditis, both in biopsy specimens and at autopsy, and the second is to try to evaluate the histological appearances that, despite the clinical findings, closely resemble the Aschoff bodies of acute rheumatism.

Intimal thickening. Of the two purposes the former has, at least in part, been achieved. Some of the appearances seen (Fig. 1) leave no doubt that incorporation of tissue derived from the organization of a thrombus may result in thickening of the intima and the presence of hæmosiderin in otherwise typical acellular thickenings suggests that many more of them may develop in a

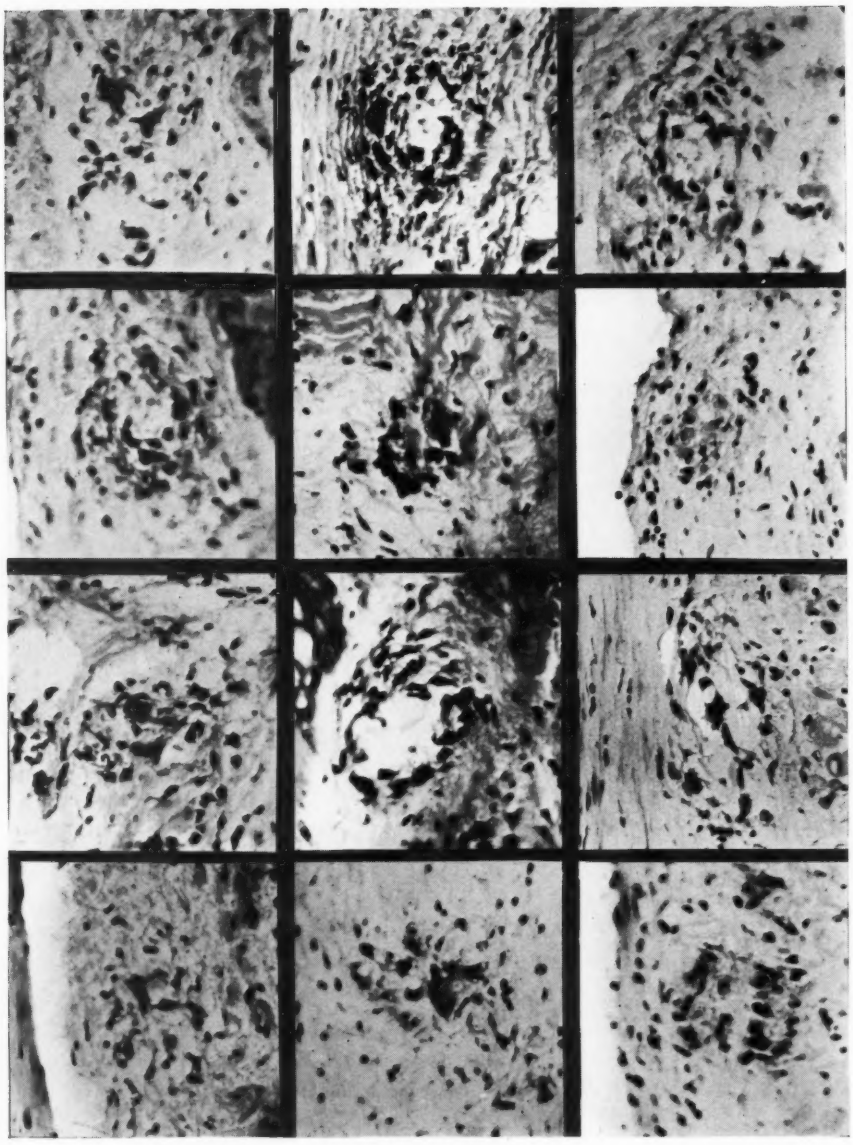


FIG. 2.—Collections of Aschoff cells in endocardium together with some fragmentation of collagen. One typical field has been photographed from each auricle showing a "probable" rheumatic lesion (see Fig. 1).

similar fashion. The frequent occurrence of elastic tissue in these lesions also suggests the same pathogenesis, since it regularly develops in organizing autogeneous thrombi in, for example, the pulmonary circulation of the rabbit (Heard, 1952). It is, however, improbable that organization of thrombi explains all these examples of intimal thickening, for the inflammatory exudates occurred predominantly in the subintimal tissue and would almost certainly give rise to fibrosis in this situation

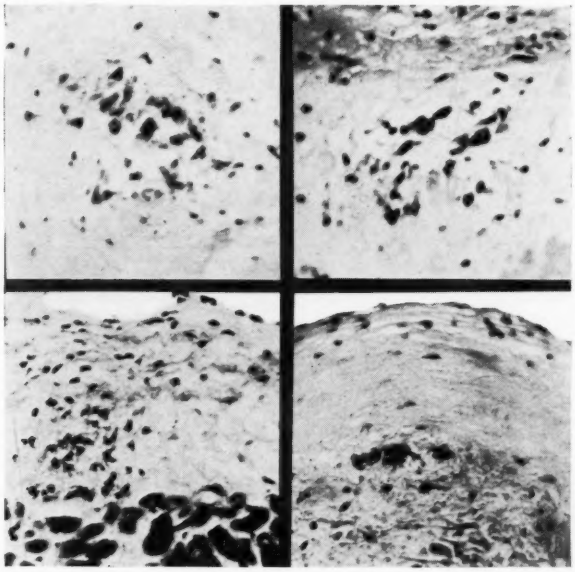


FIG. 3.—Aschoff cells in the endocardium not associated with collagenous changes. One photograph from each of 4 representative auricles showing " possible " rheumatic lesions (see Fig. 1).

on healing. It is also unlikely that the muscle cells seen in some of these thickenings were derived from metamorphosis of blood clot, the probable explanation of their presence there being that they were sequestrated from the main bulk of the myocardium as a result of inflammatory fibrosis. Finally, the mean intimal thickness in the auricles containing clot was no more than in those that did not. It may therefore be concluded that many of the intimal thickenings seen, the nodular ones in particular, are in fact derived from organization of thrombi, although this is probably not the explanation of all of them.

Appearances Suggestive of Inflammatory Disease

The cytoplasmic and nuclear changes in the cardiac muscle cells were, at first sight, some of the most conspicuous abnormalities in these sections and the clear-cut separation, between the biopsy specimens that showed them and the normal necropsy specimens that did not, suggested that they were of diagnostic significance. From the findings reported it may, however, be concluded that these appearances were largely, if not entirely, due to the fact that specimens were fixed before autolysis had produced much change in the cytoplasm and that they are not therefore significant of inflammatory or other disease.

Cubing of the endothelial cells is clearly unrelated to rheumatic carditis in these specimens,

because it was even commoner in the necropsy controls than in the biopsies and in the latter it was more frequently seen in the absence than in the presence of Aschoff cells.

Cellular foci not containing Aschoff cells were seen with equal frequency in cases with " rheumatic " lesions and those without. They were not uncommon in the pericardium in the control specimens so, although their significance is uncertain, they, too, are probably unrelated to rheumatic carditis.

Acute inflammatory lesions were seen in two cases, neither of which contained any Aschoff cells, but as there are no relevant clinical findings their significance is too uncertain for conclusions to be drawn from this observation.

Since it appears that none of the above assist in evaluating the infiltrations containing *Aschoff cells* seen in about a third of the biopsies, their intrinsic nature and situation and their association with organizing thrombi and with abnormal results to certain clinical tests will be considered in the hope that they may do so.

The minute structure of these lesions is not that of typical Aschoff bodies. All the " probable " and " possible " rheumatic lesions have been so diagnosed because they showed " mesenchymal cells " (Gross and Ehrlich, 1934) with irregular outline of which these authors state that " The most frequently occurring . . . structure of the Aschoff body is the basophilic cytoplasm with the ragged edges." They also state, however, that " no single component . . . (is) . . . by itself . . . a sufficiently characteristic feature to identify the Aschoff body " so that it deserves emphasis that this was, in fact, the only common feature of the lesions seen in these sections. Furthermore, swelling and fragmentation of collagen was seen in less than half of the " rheumatic lesions " after employing a variety of techniques specifically for the demonstration of this phenomenon. Those in which it was demonstrated are those termed " probable " lesions but it is noteworthy that in none of them was any substance with the typical tinctorial properties of fibrinoid seen. Opinions on the importance of this material in the histology of rheumatic disease are many and varied and seem to have been conditioned, at least in part, by whether the author was mainly concerned with human or experimental lesions. Thus Klinge (1933) places great importance on this substance which he illustrates so beautifully: while Gross and Ehrlich, on the other hand, in their very competent review of the lesions seen in human hearts say that " contrary to what has been stated in the literature [no references are given at this point, J.B.E.] these lesions rarely, if ever, show a fibrin constituent." Although not explicitly stated, the text suggests that this statement refers to a substance with the tinctorial properties of fibrin and is in fact an allusion to the absence of fibrinoid from the lesions that they examined. While the findings from this series agree very closely with this last statement the consensus of modern opinion is undoubtedly that true rheumatic lesions usually do show fibrinoid change of collagen (Glynn and Loewi, 1952) and the absence of it from a large series of lesions does strongly suggest that they are not indicative of active disease.

In summary these arbitrarily defined " probable " and " possible " rheumatic lesions are not histologically identical with, but do somewhat resemble, true Aschoff bodies. The former, which occurred in about one-sixth of the cases, did so rather more closely than the latter.

The distribution of these lesions, which were with one exception confined to the endocardium, is also somewhat unusual. Gross and Ehrlich (1935) examined necropsy specimens of the base of the posterior and medial walls of the left atria from 87 cases of rheumatic carditis in all stages of activity and found Aschoff bodies occurring with approximately equal frequency in both endo- and myocardium. In their earlier study (1934) of the whole heart in active rheumatism they were able in all cases to find bodies in the myocardium and, indeed, confined their attention to these, believing that they were less likely to be affected by adventitious biological and histological factors. They further state that " legitimate doubts exist concerning the identity of these lesions (in the endocardium) with those found in the interstitial tissue of the myocardium"—doubts which the findings in this series do nothing to dispel. This most important difference in the distribution of the lesions in the two series strongly suggests that they are not identical and that those found in the endocardium of the biopsies from the tip of the appendage of the atrium may have little of the

significance of the Aschoff bodies found elsewhere in the heart in the post-mortem studies of earlier authors.

Organizing thrombi occurred about twice as frequently in the biopsies in which Aschoff cells were not seen as in those in which they were and Kuschner *et al.* (1952) reported that thrombi were absent from their four cases with Aschoff bodies. It is improbable, therefore, that the presence of these cells is a reaction to the presence of thrombus in the lumen, as sometimes appears from their close relationship in the sections, but it is difficult to draw any particular conclusion from this observation.

Association of these lesions with the occurrence of "sub-clinical" rheumatic phenomena did not occur with a frequency that is significant but the results are sufficiently suggestive to justify an investigation using more complex clinico-pathological methods designed to make a more precise evaluation of the rheumatic state. The salient fact is, however—and it cannot be right to overlook it in favour of any histological signs, however striking, or of the results of clinical tests, however conclusive they may appear to be in the light of current opinion—that not only did these cases have no overt clinical signs of acute rheumatism but that they were selected for operation out of many cases examined with this end in view during a period in which it was held that active carditis was a contra-indication to that form of treatment. It can therefore be said with certainty, that these patients were not suffering from acute rheumatism, as at present understood by leading clinicians, a fact that cannot be over-emphasized in deciding the significance of these lesions.

In conclusion these lesions that were found in patients who were not suffering from clinical rheumatic fever did not have the typical structure of Aschoff bodies, and were not distributed as Aschoff bodies usually are throughout all three layers of the heart. If, however, the histological signs be accepted as representing Aschoff bodies either the specific nature of these lesions must be doubted or the clinical state to which they are supposed to correspond must be redefined. In view of (*a*) the atypical structure of these lesions, (*b*) the subsequent course of these patients which has not in any way resembled that of rheumatic fever, (*c*) the fact that the frequency with which these lesions were found in acknowledged acute cases has varied from 32 per cent (Libman, 1923) to 97 per cent (Thayer, 1931), and (*d*) the fact that there is still some doubt whether these lesions are indeed specific, it must surely be concluded that the findings in the few biopsies of heart muscle that have so far been examined, while certainly justifying doubts of the specific nature of Aschoff bodies, do not, on the other hand, justify redefining acute rheumatic fever. It is suggested that the best course is to regard the appearances seen as a new finding, the significance of which can only be elucidated by prolonged clinico-pathological investigation of, in particular, the subsequent progress of the disease and morbid-anatomical changes in the hearts in which they were found.

SUMMARY

Biopsy specimens of muscle from the left atrium of 71 patients with mitral stenosis have been examined and the results are reported.

Thickening of the intima was frequently found and was, in some cases at least, due to incorporation of organizing thrombi.

Lesions resembling Aschoff bodies were seen in the endocardium in about a third of the cases but their significance is uncertain. Reasons are given for believing that the appearances seen do not indicate active acute rheumatism. It is suggested that prolonged clinico-pathological investigation is necessary before they can be interpreted with certainty.

I wish to thank Mr. P. Brunnen for providing me with histological material from the hearts of dogs.

REFERENCES

Baker, C. G., Brock, R. C., Campbell, M., and Wood, P. (1952). *Brit. med. J.*, **1**, 1043.
Glynn, L. E., and Loewi, G. (1952). *J. Path. Bact.*, **64**, 329.
Gordon, H., and Sweets, B. S. (1936). *Amer. J. Path.*, **12**, 545.

Gross, L., and Ehrlich, J. C. (1934). *Amer. J. Path.*, **10**, 467.
—— (1935). *Amer. J. Path.*, **11**, 711.
Heard, B. E. (1952). *J. Path. Bact.*, **64**, 13.
Klinge, F. (1933). *Ergebn. allgemn. Path.*, **27**, 1.
Kuschner, M., Ferrer, M. I., Harvey, R.M., and Wylie, R. H. (1952). *Amer. Heart J.*, **43**, 286.
Lendrum, A. C. (1949). *J. Path. Bact.*, **61**, 443.
Libman, E. (1923). *J. Amer. med. Assoc.*, **80**, 813.
Thayer, W. S., (1931). *Edinburgh med. J.*, **38**, 237.

THE MECHANISM OF EFFORT SYNCOPE IN PRIMARY PULMONARY HYPERTENSION AND CYANOTIC CONGENITAL HEART DISEASE

BY

SHEILA HOWARTH AND J. B. LOWE

From the Institute of Cardiology, National Heart Hospital

Received September 25, 1952

Loss of consciousness on exertion is common in primary pulmonary hypertension, and the diagnostic value of this symptom has recently been emphasized by Dressler (1952). Yet effort syncope was recorded in only one-fifth of the 39 reported cases collected and reviewed by Dresdale *et al.* (1951). Some patients with cyanotic congenital heart disease also complain of fainting attacks occurring after exertion and one such case was reported as early as 1784 by William Hunter. There has been considerable speculation as to the mechanism of syncope in both these groups, and the purpose of this paper is to present records obtained during attacks of unconsciousness produced by effort in primary pulmonary hypertension, and to report observations made during exercise in congenital heart disease.

Material and Methods

Investigations are reported on two cases of primary pulmonary hypertension and seven cases of congenital heart disease. The clinical diagnosis was supported by cardiac catheterization and confirmed at necropsy in both those with primary pulmonary hypertension. Two cases of Fallot's tetralogy were investigated, in whom angiocardiography and cardiac catheterization supported the clinical diagnosis. The remaining five all had pulmonary hypertension, associated in four with patent ductus arteriosus and in one with ventricular septal defect. Cardiac catheterization showed that the pulmonary hypertension was severe in all five, and in every case the catheter entered the systemic circulation at the site of the shunt.

Capacitance manometers (Hansen, 1949) were used to obtain continuous brachial arterial pressure records during standing running, which was performed in every case, the outstretched arm being supported at approximately heart level. The blood pressure records showed the usual interference patterns during exercise. In two patients, recumbent during cardiac catheterization, simultaneous right heart and brachial artery pressure tracings were taken during and after exercise of the legs against a resistance.

Results in Primary Pulmonary Hypertension

Case 1. This boy gave a history of attacks of unconsciousness brought on by considerable effort during the previous year; at the time of observation he was in congestive heart failure and had a raised venous pressure and œdema. Standing running for 46 seconds caused extreme dyspnœa that prevented further exertion, but on this occasion no syncopal attack was induced. The systemic blood pressure rose during effort and had returned to the control level approximately one minute after exercise was stopped.

Case 2. This young woman complained of increasingly frequent and severe attacks of effort syncope during the previous nine months. The brachial artery pressure during and after standing running is shown in Fig. 1. During exertion there was a decrease in both systolic and diastolic

pressures: after exercise, both fell and the pulse pressure diminished. During the period of falling blood pressure the patient was supported in the erect position and, after complaining of dizziness, lost consciousness. Bradycardia occurred at the end of the record when the blood pressure was at its lowest. On a subsequent occasion, an electrocardiogram was taken before and after exercise.

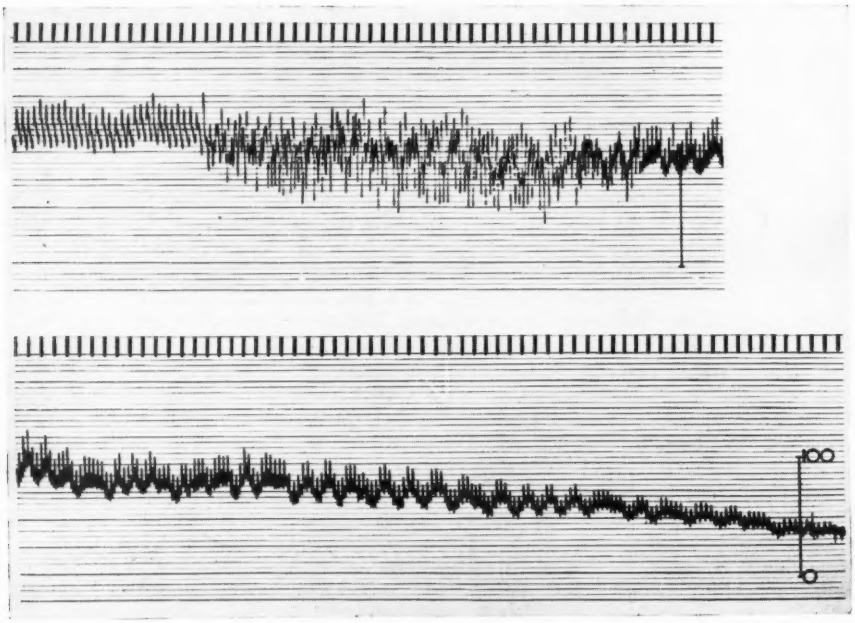


FIG. 1.—Case 2. Syncopal attack in primary pulmonary hypertension. Continuous brachial arterial pressure record before, during, and after standing running (indicated by interference on pressure record). Time scale (top) in this and subsequent records in seconds. Calibrations in mm. Hg.

The tracing (Fig. 2) shows the tachycardia immediately after effort, and the onset of sinus bradycardia some 1½ minutes later when the patient complained of faintness and when the blood pressure had presumably fallen to a low level. In an attempt to elucidate the mechanism of the attacks, further observations were made during cardiac catheterization (Fig. 3). After exercise, brachial arterial pressure fell gradually and loss of consciousness resulted as before. Bradycardia occurred when the mean pressure had reached about 30 mm. Hg. The pulmonary artery pressure rose steeply on effort; and at the end of exercise, when the catheter had slipped back into the right ventricle, the systolic pressure in this chamber was approximately 140 mm. Hg. During the time when the systemic arterial pressure was falling, the pulse pressure in the right ventricle decreased and the diastolic pressure rose by 10 to 15 mm. Hg. These results are consistent with acute failure of the right ventricle. Systemic blood pressure, right ventricular systolic and pulse pressures, and heart rate then increased spontaneously. Recovery was, however, interrupted by a period of grossly disordered rhythm, accompanied by cessation of respiration, before all readings returned to normal.

RESULTS IN CONGENITAL HEART DISEASE

Fallot's Tetralogy. Case 3. This boy with Fallot's tetralogy squatted when breathless but did not give a history of effort syncope. Resting arterial oxygen saturation was 74 per cent. Although

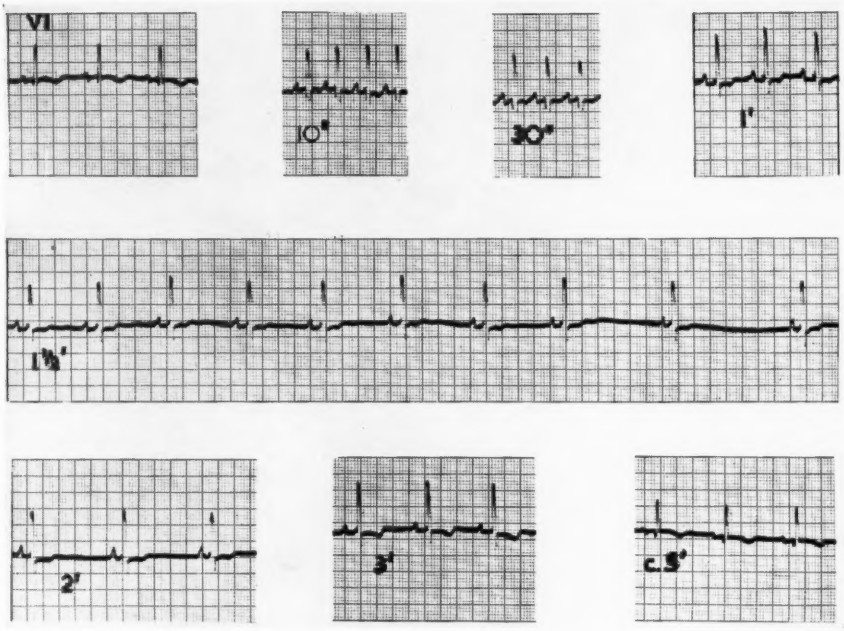


FIG. 2.—Case 2. Electrocardiogram (lead VI) taken before and at stated intervals after exercise.

standing running was continued to the limit of his endurance and resulted in extreme dyspnœa and a considerable increase in cyanosis, no fall in systemic pressure was seen either during or after exercise.

Case 4. Cyanosis at rest was inconspicuous in this patient with Fallot's tetralogy, but ever since infancy exertion had caused cyanosis and frequently loss of consciousness. Standing running induced a syncopal attack (Fig. 4). Systolic and diastolic brachial artery pressures rose during effort but in the period after exercise there was a gradual decline in both, together with a decrease in pulse pressure. During the last part of the observation the patient had to be supported on account of dizziness, and he lost consciousness some five minutes after the end of exertion when the mean blood pressure was just over 50 mm. Hg. Bradycardia appeared at the end of the tracing but the record at this point was unsatisfactory and is not shown. It is noteworthy that the patient was still markedly cyanosed and also dyspnœic when loss of consciousness supervened.

Patent Ductus Arteriosus with Pulmonary Hypertension. Case 5. This young woman gave a clear history of effort syncope. Strenuous exercise was followed by severe breathlessness and chest pain of some two minutes duration, and she would then sometimes lose consciousness. Syncopal attacks had occurred during the previous two years and had been most frequent in the summer months. She was not cyanosed at rest, when arterial oxygen saturation was 90 per cent, but had been told that she became blue on effort. Although standing running not only resulted in severe dyspnœa and striking cyanosis but also caused her to complain of faintness, there was no fall in systemic blood pressure (Fig. 5). During cardiac catheterization, exercise again failed to induce a syncopal attack. Both systemic and pulmonary arterial pressures rose during exertion, returning to control levels afterwards.

Of three other similar patients (Cases 6, 7, and 8) with patent ductus arteriosus and pulmonary

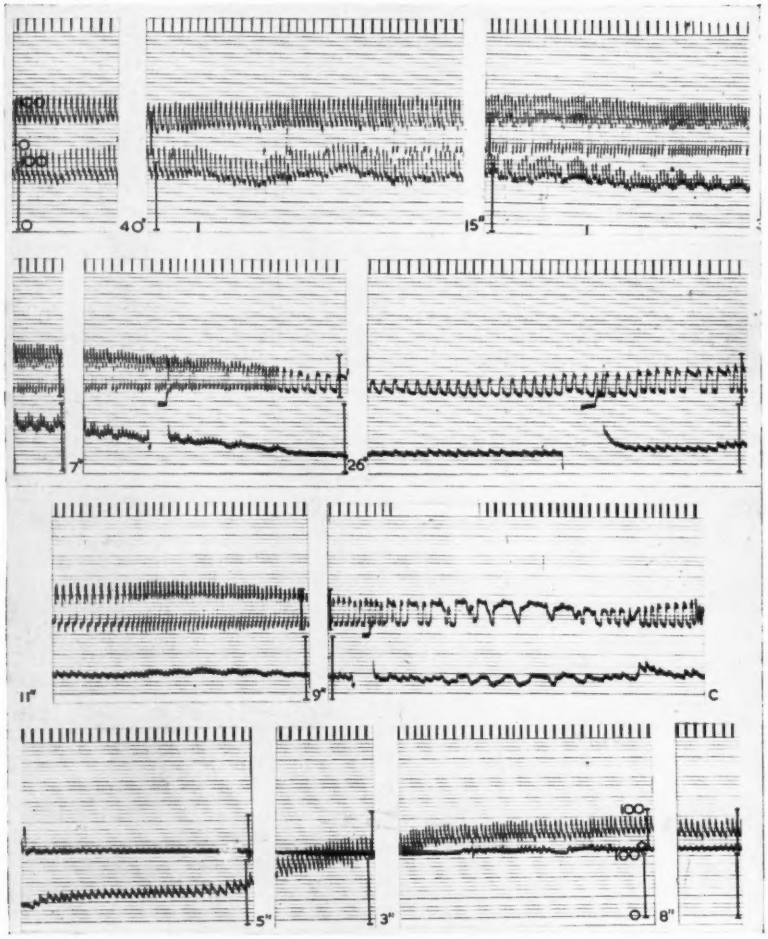


FIG. 3.—Case 2. Continuous record of syncopal attack induced during cardiac catheterization. Beginning and end of exercise marked by signals at bottom of tracing. Upper record: pressure in (a) pulmonary artery (first two strips) (b) right ventricle (six strips) and (c) right atrium (remainder of tracing). Lower record: brachial artery pressure. Breaks in continuous record indicated by figures at bottom of tracing. For full description, see text.

hypertension sufficiently severe to cause shunt reversal and cyanosis on exertion, only one gave a history of faintness after effort. This had occurred when strenuous effort had caused extreme breathlessness and cyanosis. The response of the brachial artery pressure to vigorous standing running was observed in all three: in none did faintness or dizziness result, and in none was there a fall in pressure either during or after exercise.

Ventricular Septal Defect with Pulmonary Hypertension. Case 9. This patient had suffered from transient attacks of giddiness and cyanosis on effort for seven years, and for four years syncopal

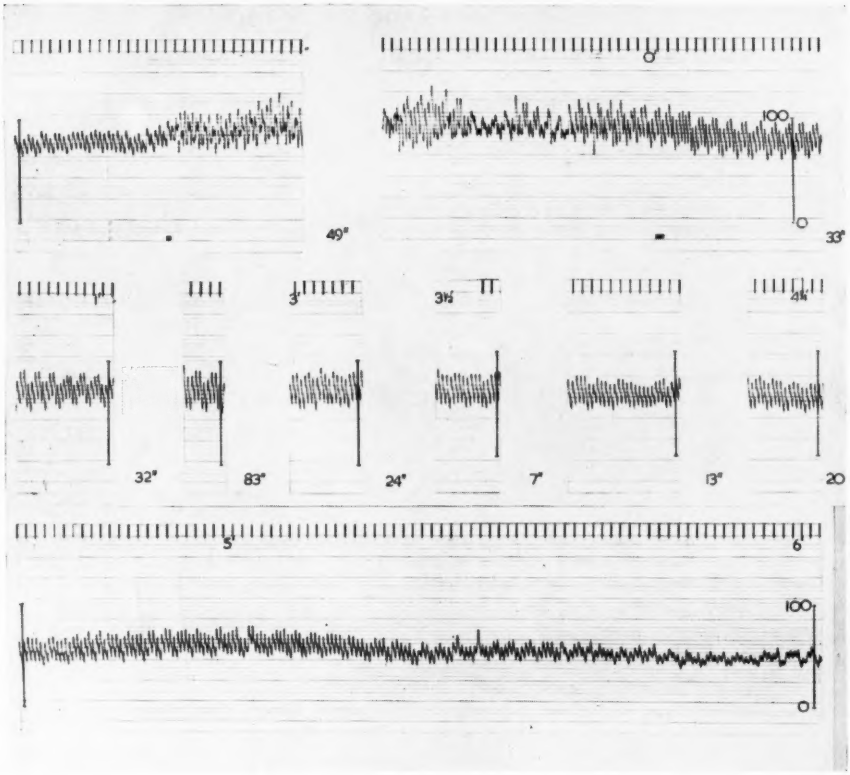


FIG. 4.—Case 4. Fallot's tetralogy. Brachial arterial blood pressure record during a syncopal attack induced by exercise. Figures below time marker are minutes after exercise. Consciousness was lost about 5 minutes after exercise ended.

attacks had occurred after severe exertion. Brachial artery pressure was recorded during two periods of standing running. On the first, moderate exercise for two minutes resulted in cyanosis and a transient fall in diastolic pressure during the first ten seconds after exertion (Fig. 6a). On the second occasion more strenuous effort was undertaken for approximately 3¼ minutes (Fig. 6b). During exertion the diastolic pressure fell but there was no decrease in pulse pressure. About 30 seconds after exercise the diastolic pressure started to rise again but had not returned to its initial level three minutes later. During exertion arterial oxygen saturation decreased from the resting level of 92 to 51 per cent. Dyspnœa persisted for some minutes afterwards but the patient did not feel faint.

DISCUSSION

In conditions where cardiac output is relatively fixed, peripheral vasodilatation induced by exercise might be expected to cause a fall in systemic blood pressure. This should occur towards or at the end of exercise when vasodilatation, especially of muscle vessels, is maximal. The syncopal attacks of primary pulmonary hypertension might, on *a priori* grounds, be explained in this manner, since the high pulmonary resistance might limit the increase in cardiac output on exercise.

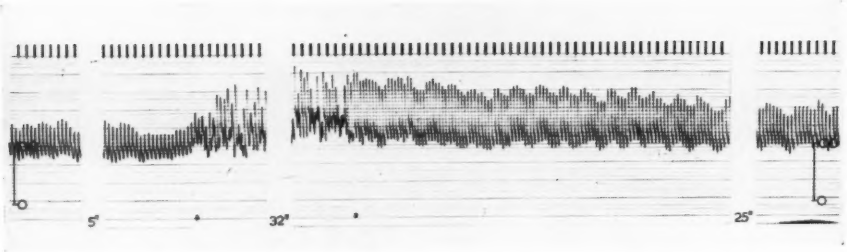


FIG. 5.—Case 5. Pulmonary hypertension with patent ductus arteriosus. Patient became cyanosed and complained of dizziness after effort: no fall in blood pressure was recorded.

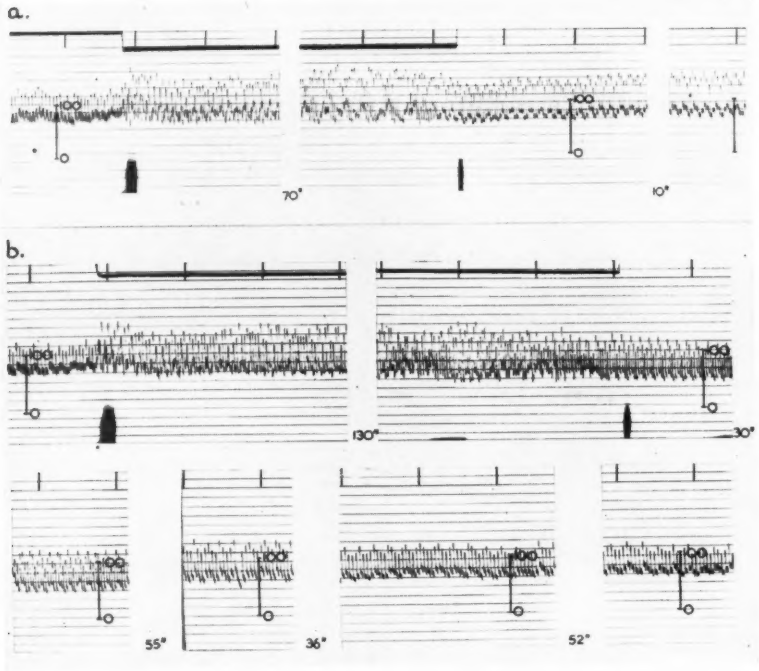


FIG. 6.—Case 9. Pulmonary hypertension and ventricular septal defect. (a) Exercise for two minutes resulted in cyanosis with transient fall in blood pressure. (b) More strenuous exercise caused a symptomless fall in diastolic pressure with marked cyanosis. Time scale in both records is 10 seconds.

Continuous blood pressure records taken during effort syncope in this condition, however, show that the fall in systemic pressure leading to unconsciousness is gradual and progressive from the end of exercise. Simultaneous records of right heart and systemic blood pressures during an attack show acute right heart failure with diminishing right heart output to be the cause of the falling blood pressure. The steep rise in pulmonary arterial pressure on exercise is presumably the main factor precipitating failure of the right ventricle.

In the cases reported here, syncope did not occur during exercise, but followed after a varying

period, and the clinical observations correlated well with the observed blood pressure records, which showed the hypotension to be gradual and progressive. In the more severe or terminal type of case, however, it might be expected that the amount of exercise required to induce acute right heart failure would be less. Such a case was observed two days before death, when foot movements resulted in a steady and continuous fall in the recorded blood pressure, leading to syncope after one minute while exercise was still in progress.

The pallor, low blood pressure, and bradycardia seen during this form of syncope resemble the vasovagal faint, but the mechanism is different. In vasovagal fainting, sudden hypotension results from a fall in peripheral resistance due to muscle vasodilatation, while cardiac output remains relatively unchanged (Barcroft *et al.*, 1944). Conditions that cause vasovagal fainting are those in which the filling pressure of the heart is reduced (Brigden *et al.*, 1950). In the effort syncope of primary pulmonary hypertension the diastolic pressure rises on the right side of the heart. No studies have yet been made on the peripheral circulation in the latter group.

Bradycardia occurs when the blood pressure reaches low levels both in the vasovagal and exertional faints. It has been suggested by Dressler (1952) that in pulmonary hypertension this is a reflex from the pulmonary artery, where a rise in pressure has been shown experimentally in animals to cause cardiac slowing (Parin, 1947; Aviado *et al.*, 1951). In vasovagal fainting where pulmonary arterial pressure falls (Howarth and Lowe, unpublished observations) and during syncope in Fallot's tetralogy, this explanation would appear unlikely. Certainly vasovagal fainting may be induced in the atropinized subject without alteration in heart rate (Lewis, 1932; Howarth, 1952). It is suggested that bradycardia in both types of fainting is secondary to the low blood pressure state.

In cases where a shunt existed and a history of syncope was present, resting arterial oxygen saturation was relatively normal. On effort, considerable cyanosis was either observed or measured. A sudden fall in arterial oxygen tension may cause loss of consciousness in the normal subject, with fall in blood pressure, bradycardia, and muscle vasodilatation (Anderson *et al.*, 1946). A sudden decrease in arterial oxygen saturation may well be a factor in the mechanism of syncope when a right to left shunt is present.

Summary

Blood pressure records were obtained in cases of primary pulmonary hypertension and Fallot's tetralogy during induced syncope after exertion. Blood pressure fell gradually and not precipitously after exercise. Sinus bradycardia and loss of consciousness occurred when the systemic pressure reached low levels.

A syncopal attack was induced in a case of primary pulmonary hypertension during cardiac catheterization. As the systemic pressure fell, the pulse pressure in the right ventricle decreased with a rise in the diastolic pressure.

These results are compatible with acute failure of the right ventricle.

Four cases of pulmonary hypertension with patent ductus arteriosus were exercised; no syncopal attack was induced. One case of pulmonary hypertension with patent interventricular septum exhibited a symptomless fall in systemic diastolic pressure after exercise, associated with considerable cyanosis.

It is suggested that sudden decrease in arterial oxygen saturation may be a factor causing loss of consciousness in cases with a right to left shunt.

We are indebted to Mr. J. G. Davies for technical assistance. The cases studied were under the care of the physicians to the National Heart Hospital.

References

Anderson, D. P., Allen, W. J., Barcroft, H., Edholm, O. G., and Manning, G. W. (1946). *J. Physiol.*, **104**, 426.
Aviado, D. M., Li, T. H., Kalow, W., Schmidt, C. F., Turnbull, G. L., Peskin, G. W., Hess, M. E., and Weiss, A. J. (1951). *Amer. J. Physiol.*, **165**, 261.
Barcroft, H., Edholm, O. G., McMichael, J., and Sharpey-Schafer, E. P. (1944). *Lancet*, **1**, 489.
Brigden, W. W., Howarth, S., and Sharpey-Schafer, E. P. (1950). *Clin. Sci.*, **9**, 79.
Dresdale, D. T., Schultz, M., and Michton, R. J. (1951). *Amer. J. Med.*, **11**, 686.
Dressler, W. (1952). *Amer. J. med. Sci.*, **223**, 131.
Hansen, A. Tybjaerg (1949). *Pressure Measurement in the Human Organism.* Teknisk Forlag, Copenhagen.
Howarth, S. (1952). *Shock and Circulatory Homeostasis.* Green, H. D., Editor. *Trans. 1st. Conf. New York, Josiah Macy Jr. Foundation*, 1951 (p. 123).
Hunter, W. (1784). *Med. Obs. Soc. Physicians, Lond.*, **6**, 299.
Lewis, T. (1932). *Brit. med. J.*, **1**, 873.
Parin, V. V. (1947). *Amer. J. med. Sci.*, **214**, 167.

MITRAL INCOMPETENCE

BY

WALLACE BRIGDEN AND AUBREY LEATHAM

From the Cardiac Department of the London Hospital and the Institute of Cardiology, National Heart Hospital

Received August 28, 1952

We have investigated 30 adult patients in whom we believe mitral incompetence due to endocarditis was the only cardiovascular abnormality. Ten patients died and the diagnosis has been confirmed at necropsy in nine (see Appendix). Our aim has been to determine the natural history, symptoms, and signs of this uncommon lesion and to evaluate these signs in order to assess the degree of incompetence in the presence of mitral stenosis and of other valve lesions.

Historical Note

Corvisart (1813) and his pupil Laennec (1829) described signs that they attributed to disease of the mitral valve. Both recognized a "purring thrill" and Laennec described a rasping apical murmur, but there is no evidence that they appreciated the timing of these signs in the cardiac cycle. Hope (1849) was the first to relate the systolic murmur and thrill to mitral regurgitation—"when the valve is permanently patescent admitting of regurgitation the first sound likewise is attended with a murmur," and on another occasion, ". . . when blood regurgitates into the auricle, this cavity suffers in a remarkable degree." For the rest of that century apical systolic murmurs tended to be regarded as organic and caused by mitral regurgitation. A change of attitude to these murmurs must largely be attributed to Graham Steell (1906) and Sir James Mackenzie (1916), though Potain (1894) had criticized English and German authors for believing that functional mitral incompetence accounted for all apical systolic murmurs not due to mitral valve disease. Graham Steell recognized that incompetence frequently accompanied mitral stenosis but doubted if it was of any significance: he stated that it was impossible to give a description of mitral incompetence for it occurred in such a variety of conditions. He continually emphasized the importance of muscle failure rather than primary disease of the valve and said that no one ever died from mitral regurgitation. Mackenzie also held these views. This teaching was continued by Lewis (1933) who said that to regard any distinct systolic apical murmur as meaning a diseased valve was indefensible. Cabot (1926) admitted the existence of mitral incompetence but emphasized its rarity—"even in rare cases wherein mitral regurgitation without stenosis does exist, there are no physical signs by which it can be recognized or reasoned out, so that a diagnosis of mitral regurgitation without stenosis is never justified." This teaching corrected the habit of diagnosing heart disease on hearing a systolic murmur at the apex and prevented much unwarranted cardiac invalidism (Evans, 1948). In the last thirty years many writers (Sprague and White, 1926; Fishberg, 1940; Master, 1948) have considered that the apical systolic murmur has been unjustifiably relegated to an insignificant position. In the Harveian Oration of 1945 Parkinson considered that the diagnosis of mitral incompetence as a rheumatic valvular lesion should be made, though never again as a rival of mitral stenosis.

Clinical Method

These 30 patients have been seen over a period of three years. With two exceptions physical examination and X-ray screening were carried out by both of us. Electrocardiograms were taken in all cases, and logarithmic (Rappaport and Sprague, 1942) or high frequency (Leatham, 1949) phonocardiograms were recorded synchronously at the mitral and pulmonary areas in all but three. Only patients with a loud mitral systolic murmur (at least of grade four intensity using the classification of Freeman and Levine, 1933) were considered, and they were included if there was

no ischæmic heart disease, hypertension (B.P. over 160 systolic or 100 diastolic, with the exception of necropsy Case 29), or anæmia, and no evidence of other valve lesions. In fact all those where there was a possibility of functional mitral incompetence have been excluded. The patients under consideration were examined on several occasions and excluded if a presystolic or mid-diastolic murmur was heard at any time, unless necropsy showed no mitral stenosis. Patients with a history suggesting rheumatic fever within five years and those under 20 have also been excluded as we wished to confine our observations to those with relatively static disease; likewise patients with bacterial endocarditis have only been included when it was known that there was a loud apical systolic murmur, satisfying the conditions we have mentioned, before the onset of that infection. By rigorously applying these negative criteria we were left with a group that shows a constant pattern of physical signs and clinical behaviour.

Clinical Features

The principal clinical features of the 30 patients are shown in Table II. Sixteen were between 50 and 60 years old and the oldest was 75. The natural history of this group was longer and more favourable than that of mitral stenosis where the greatest mortality lies between the ages of 30 and 45 (Baker and Musgrave, 1947). Eight of our patients were known to have a murmur for more than 25 years, the date being settled by an examination for military service in the First World War.

The well-known sex preponderance of women in cases of mitral stenosis (White, 1947) is in contrast with this series in which 25 of the 30 patients were men. Male preponderance in cases of organic mitral incompetence is also seen in Cabot's series of six autopsies where five were in men. We could find no evidence that selection explained this incidence and it appears to be a special feature of the condition. A similar male preponderance is found in isolated aortic stenosis (3 to 1 by Kumpe and Bean, 1948; up to 2·5 to 1 by Karsner and Koletsky, 1947).

A history of rheumatic fever was given by three of the five women, but by only four of the twenty-five men which is much lower than the incidence of 50 to 60 per cent given by various authors for mitral stenosis.

Many authors have drawn attention to the relatively frequent occurrence of bacterial endocarditis in patients with an isolated loud mitral systolic murmur. Thus, Sprague (1930) stated that patients with rheumatic heart disease in whom mitral incompetence persisted without the development of stenosis of marked degree were more likely to acquire bacterial endocarditis than those in whom the valve became obviously stenosed in a few years. He described the necropsy findings in 20 cases of bacterial endocarditis; the mitral valve was involved in 19 of these and in no less than 18 the valve was more than 8 cm. in circumference. Cates and Christie (1951) found stenosis in only 2 of 29 necropsies of lone mitral valve disease in a large series of patients with bacterial endocarditis. Ten of our 30 patients had bacterial endocarditis which was treated with penicillin; two of these had more than one attack and five died (necropsy in Cases 2, 15, 21, and 30). A loud apical systolic murmur had been heard in all before the bacterial endocarditis supervened. Dental extraction or other operative procedures appeared to initiate the infection in three cases. This high incidence of bacterial endocarditis is in contrast with its relative rarity in pure mitral stenosis, and cannot be explained by the longer natural history of mitral incompetence for bacterial endocarditis was not confined to patients in the older age group. The admission to hospital of patients with bacterial endocarditis has resulted in a large number showing this complication, but this does not affect its relative frequency in mitral incompetence compared with mitral stenosis. In view of the considerable risk of bacterial endocarditis in this group we agree with Master (1948) that prophylaxis with penicillin should be used invariably for such patients when undergoing any form of dental or surgical treatment.

Heart failure occurred in nine patients of whom eight died, six of them within a year of their first examination. Only two of the remaining patients complained of dyspnœa on exertion. It seems that heart failure is late in onset, but may progress rapidly in spite of treatment.

Symptoms and Signs. The only symptom of mitral incompetence, uncomplicated by bacterial endocarditis or heart failure, is palpitation and this deserves further comment. It is common experience that palpitation is a frequent symptom of neurotic ill-health. Yet palpitation was the presenting symptom in 15 of our patients and this was found to be due to frequent extrasystoles. Electrocardiograms showed that there were multiple right or left ventricular extrasystoles in all of these patients.

The pulse was usually normal; it was not small as in aortic stenosis or mitral stenosis and was never collapsing, but occasionally it appeared to be large. Five patients showed auricular fibrillation. The increased and sustained apical impulse of an enlarged left ventricle was frequently seen and more often felt, but was never as obvious as it may be in aortic valve disease or hypertension. Eighteen of 25 of our patients had clinical evidence of an enlarged left ventricle. In some a diastolic-filling wave coinciding with the third heart sound was seen and felt at the apex. Accelerated filling of the left ventricle in mitral incompetence has been demonstrated by roentgenkymography (Hirsch and Gubner, 1936). No patient had the palpable accentuated first sound of mitral stenosis or any sign of right ventricular hypertrophy. An apical systolic thrill was felt in 19; this high incidence reflects the selection of patients with loud murmurs.

Auscultation provided the most important evidence of mitral valve disease. The first sound was normal; it could usually be distinguished from the systolic murmur at the apex and was never accentuated as in mitral stenosis: these points were confirmed on the phonocardiogram (Fig. 1 and 2). Furthermore, the delay of the first sound in relation to the QRS complex that is usually

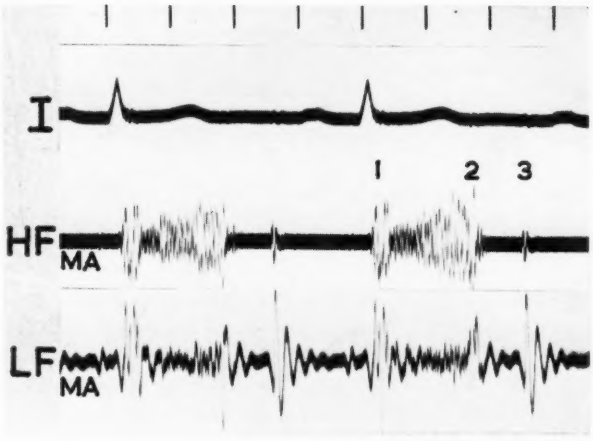


FIG. 1.—Synchronous high (HF) and low (LF) frequency phonocardiograms recorded from the apex (MA) in Case 9. A normal first sound is followed by the long systolic murmur showing a crescendo in late systole. The second sound is included in the systolic murmur at the apex in the high frequency recording but is shown in the low frequency recording. The third sound is accentuated. The time interval in this and subsequent records is 0·2 sec. (and 0·04 sec.).

present in mitral stenosis (Weiss and Joachim, 1911; Cossio and Berconsky, 1943) was not found in this series. The systolic murmur started at the first sound and it was always loud (the significance of the loudness of the systolic murmur could not be assessed in the 21 selected patients, but it was equally loud in each of the 9 necropsy cases). It was loudest at or near the apex radiating to the axilla and left scapula, a feature well known to Gee in 1893; it was sometimes heard in the region of the right scapula. Though loud at the left sternal edge the murmur was much diminished to the

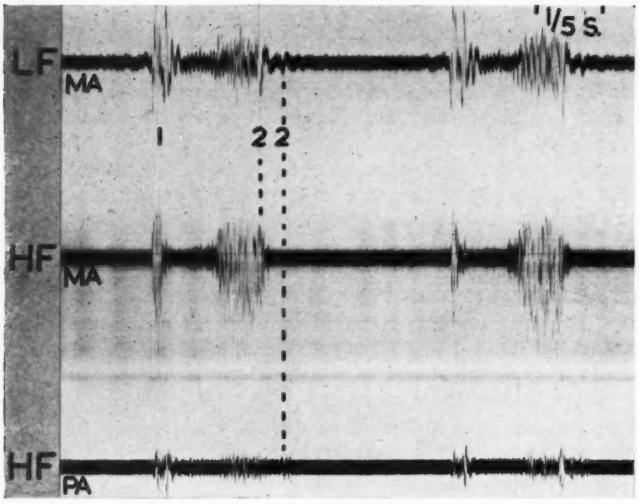
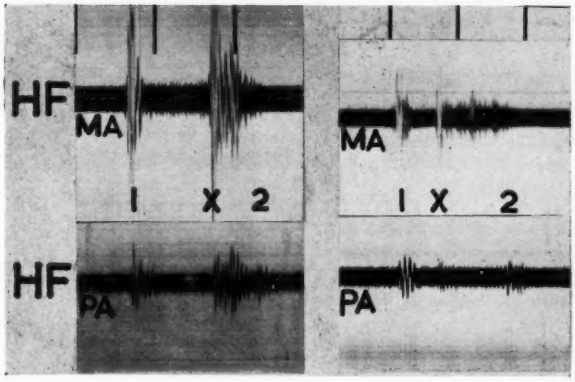


FIG. 2.—Synchronous phonocardiograms, low and high frequency in the mitral area, and high frequency in the pulmonary area (PA). Case 4. There are early systolic vibrations of low intensity (inaudible) of and a late systolic murmur going up to the aortic component, the second sound, though, finishing before the pulmonary component.

right of the sternum and was either absent or faint and never more than grade 2 in the aortic area. The systolic murmur was long (pansystolic), starting immediately after the first sound and always continuing up to and including the second sound (Fig. 1). While it may be difficult to distinguish the length of the systolic murmur by auscultation alone, much reliance may be placed on the apparent absence of the second sound exactly at the apex where the systolic murmur is loudest; the second sound is easily heard in all other areas. When the second sound was split the systolic murmur extended to the aortic component but not to the later pulmonary component; this may explain the statement by Wiggers (1923), that the systolic murmur sometimes finished before the second sound. In some patients the murmur had a crescendo quality and in three it seemed to be confined to late systole; occasionally the late crescendo was preceded by a systolic click (Fig. 3). Phonocardiograms established this close relationship between the systolic murmur and sounds and showed an increase in intensity in late systole in 12 cases (Fig. 1); there were always some vibrations in early systole but these were very small in the three patients in whom only a late systolic murmur was found on auscultation (Fig. 2). One patient was thought to have a late systolic murmur in 1940 which had become pansystolic eight years later (Case 17). One patient who came to necropsy had been diagnosed as having an innocent late systolic murmur (Case 5). Bedford (1945) has emphasized, though without graphic evidence, that late systolic murmurs are not always innocent, and Wood (1950) has stated that they may be a sign of mitral incompetence; their presence in children with rheumatic carditis has been noted by Miller and Wedum (1949). It may at least be stated that a late systolic murmur is no guarantee that the patient will not develop bacterial endocarditis.

The systolic murmur of aortic stenosis may be loud at the apex and may be difficult to distinguish from that of mitral incompetence; in fact three patients who came to necropsy had been diagnosed previously as aortic stenosis. The murmur of aortic stenosis is usually loud in the aortic area and is short and confined to mid-systole, finishing before the aortic second sound (Alzamora-Castro, 1947, Fig. 4). In aortic stenosis of slight or moderate degree when the pulse is normal, the left ventricle not greatly enlarged, and aortic valve calcification absent, attention to the distribution



A B

FIG. 3.—Phonocardiograms recorded from Cases 26 and 20 (Fig. A and B) showing a late systolic murmur preceded by a systolic click (x).

and timing and quality of the murmur can differentiate the two conditions and a phonocardiogram will give confirmatory evidence (Leatham, 1951). Ventricular septal defects may be distinguished by a more centrally placed murmur and the absence of systolic expansion of the left auricle.

Patients with a mid-diastolic or a presystolic (auricular systolic) murmur were excluded from this series (except necropsy cases). On careful auscultation there was a soft, short early diastolic murmur internal to the apex or near the pulmonary area in 13 cases (Fig. 5 and 6). It was present in five cases subsequently examined at necropsy; not one showed disease of the semilunar valves although it is appreciated that this does not exclude a slight functional incompetence, especially of the pulmonary valve. This short early diastolic murmur might sometimes be due to the continuation of mitral regurgitation into diastole after aortic valve closure and until the auricular and ventricular pressures are equalized (Wiggers and Feil, 1921). Such an explanation is supported by the electrokymographic findings of Luisada and Fleischner (1948) who showed continuation of auricular

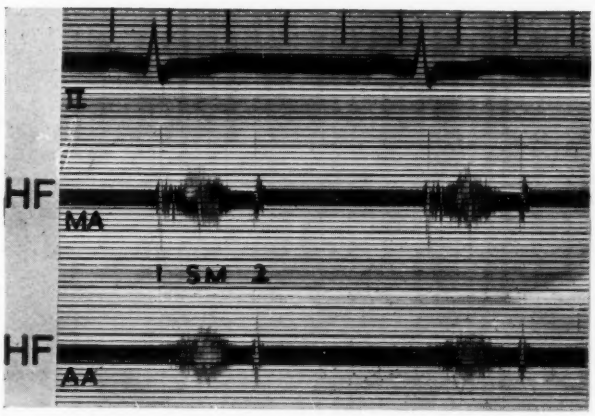


FIG. 4.—Phonocardiogram of a patient with aortic stenosis. The systolic murmur finishes before the second sound.

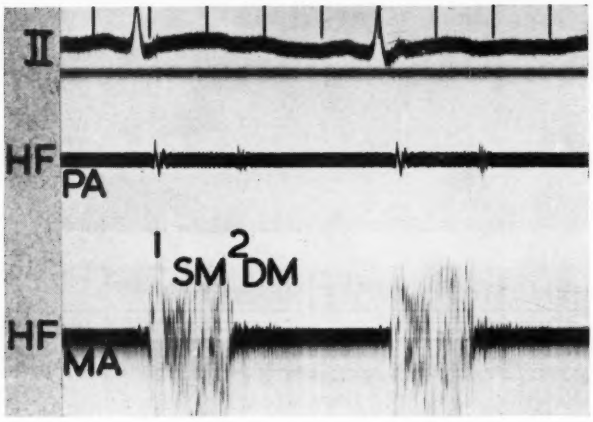


FIG. 5.—Phonocardiogram recorded from Case 6 showing the long systolic murmur and an early diastolic murmur.

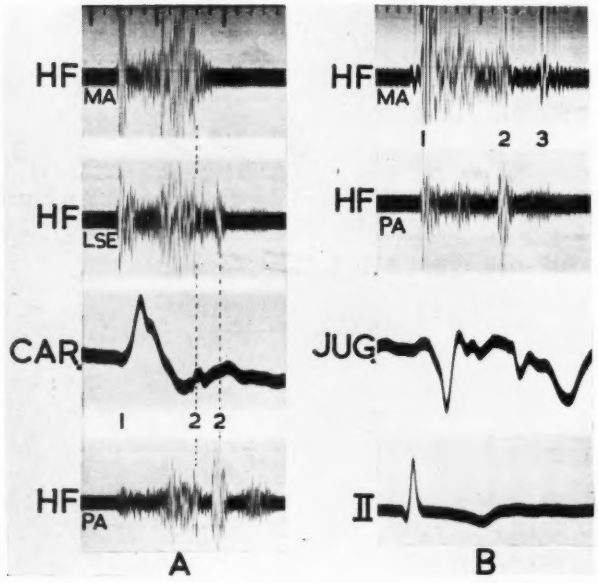


FIG. 6.—Two further cases of mitral incompetence illustrating the pansystolic murmur reaching the aortic component of the second sound. In (A) the separate pulmonary component can be seen 0·07 sec. later, and after the dicrotic notch of the carotid (CAR) pulse. The short, early diastolic murmur is shown in (A) and (B) and the third sound at the mitral area in (B). (Case B by kind permission of Dr. Charles Baker.)

expansion after the second sound. Another possible cause is the elastic recoil of the over-distended auricle resulting in a flow through the mitral valve in early diastole.

In mitral valve disease the second sound, which is often split into aortic and pulmonary components, may be followed closely by the mitral snap (opening snap), and slightly later by the third sound marking the entry of blood into the ventricles and initiating the mid-diastolic murmur when this is present. Splitting of the second sound is due to delay in the pulmonary component and is maximal during inspiration; this sound is loudest at the pulmonary area and poorly conducted elsewhere. The width of the split is increased by right bundle branch block and the intensity of the pulmonary component is exaggerated by pulmonary hypertension. Under these circumstances the pulmonary component of the second sound may be mistaken for the mitral snap. This sound, specific to mitral valve disease, is usually loudest internal to the apex and at the lower end of the sternum, but when very loud may be well conducted to the mitral, pulmonary, and aortic areas. It is high pitched, often loud, and resembles the second sound in quality. The mitral snap is maximal in expiration and its timing is not affected by inspiration when splitting of the second sound is greatest. However, the only certain method of distinguishing the mitral snap from the pulmonary component of the second sound is to hear and record all three sounds. Often two " second sounds " can be heard in mitral valve disease but in the pulmonary area and lower left sternal edge during inspiration the first of these two sounds splits into aortic and pulmonary components and the later sound is the mitral snap (Fig. 7). The third heart sound is later in diastole and has an entirely different quality; it is longer, lower pitched, and usually confined to the apex (Fig. 1). The auscultatory signs of pure mitral stenosis are illustrated in Fig. 7.

The second sound in the pulmonary area was frequently split. Thirteen of 20 patients in whom phonocardiograms were recorded in the pulmonary area showed a degree of splitting that was usually greater than normal (Fig. 2 and 6A); none of these had bundle branch block. The first component of this split sound was always thought to be aortic, and it is therefore suggested that left ventricular systole was shorter than normal. The diminished resistance to left ventricular outflow due to mitral regurgitation is probably the explanation of this shortened systole.

The pulmonary component of the second sound was not increased in intensity in any patient in this series and none showed clinical evidence of pulmonary hypertension.

The mitral snap which is frequently heard in mitral stenosis (Fig. 7) was not heard or recorded

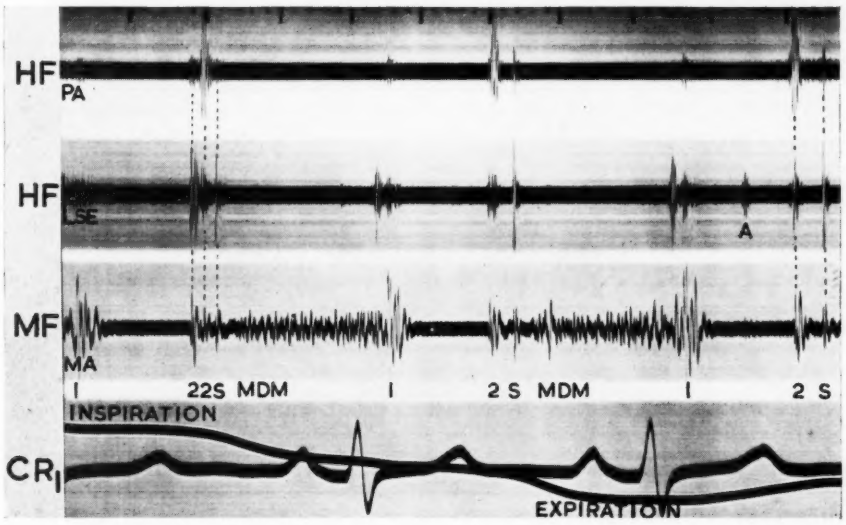


FIG. 7.—Phonocardiogram of a patient with pure mitral stenosis showing a late first sound (nearly 0·1 sec. after R wave), split second sound (during inspiration), opening snap (S) (larger in expiration), and long mid-diastolic murmur (MDM). A=artefact; LSE=lower left sternal edge; MF=medium frequency phonocardiogram.

in a single patient. We conclude that this clear sound is related to the existence of stenosis rather than incompetence of the mitral valve. The third heart sound, which in our experience is rarely heard or recorded in pure mitral stenosis, was audible at the apex in 15 cases (Fig. 1) and shown on the phonocardiogram in all these and in four more in whom it was inaudible; it might have been normal in five who were young. Sprague and White (1926) have noted its frequency in mitral incompetence. It was not possible to relate the third sound to any other signs, but it was probably due to increased filling of the left ventricle.

A short mid-diastolic murmur was heard and confirmed on the phonocardiogram in only one of the necropsy cases (Case 12). This murmur probably arose from turbulence, like the Carey Coombs murmur in cases of acute rheumatic valvulitis, or from increased blood flow as in patent ductus arteriosus or ventricular septal defect. However, an obvious mid-diastolic murmur must exclude the diagnosis of *pure* mitral incompetence.

The principal features of pure mitral stenosis are contrasted with those of pure mitral incompetence in Table I, and the findings in the patients with mitral incompetence are shown in Table II.

TABLE I

THE PRINCIPAL FEATURES OF PURE MITRAL STENOSIS CONTRASTED WITH THOSE OF PURE MITRAL INCOMPETENCE

	Mitral Stenosis	Mitral Incompetence
Sex	Women preponderant	Men preponderant
History of rheumatic fever, etc.	In over half	Uncommon
Bacterial endocarditis	Uncommon	Common
Heart failure	Common	Late
Pulse	Small	Normal or increased
Apex beat	Palpable first sound	Suggests left ventricular hypertrophy
First sound	Loud	Normal
Second sound	Normal at apex	Inaudible at apex, being included in systolic murmur
Opening snap	Frequent	Absent
Third sound	Infrequent	Frequent, often loud
Murmurs	Mid-diastolic Presystolic With or without thrill	Systolic, loud and long : may be maximal in late systole With or without thrill
X-rays		
Enlargement of left auricle	All degrees	All degrees—usually slight or moderate
Systolic backward movement of left auricle	Frequent	Frequent
Systolic expansion of left auricle (as shown by obvious pulsation in all views)	Never	Essential for X-ray diagnosis
Electrocardiogram		
P wave	Frequently large and bifid	Normal
Ventricular preponderance	Tendency to right	Tendency to left

RADIOLOGY

Obvious systolic expansion of the left auricle is the most important radiological sign of mitral incompetence.

In the normal heart left ventricular systole is seen as an inward movement of the apex and left border of the heart; above, the pulmonary artery and aorta move outwards in systole. The right auricle forming the right border of the heart also moves inwards in systole. The right auricular border joins that of the superior vena cava in 80 per cent of normal subjects (Hirsch and Gubner, 1936), and the pulsation here is not very obvious on fluoroscopy. In some normal subjects, especially in the older age groups, the upper right border of the heart is formed by the aorta which moves outwards in systole. In the right and left oblique views the left auricle moves inwards in systole in 90 per cent of healthy subjects; in the rest there is no decisive movement though rarely the pulmonary artery region of the posterior border moves slightly

TABLE II

A SUMMARY OF OUR FINDINGS IN 30 PATIENTS WITH PURE MITRAL INCOMPETENCE

Number	Sex	Age	Length of history in years	Rheumatic fever, etc.	Bacterial endocarditis	Presenting symptom	Heart Failure	Signs at Apex				B.P.	Phono.		Radiology				Electrocardiogram			
								L.V. impulse *	Systolic murmur	Thrill	3rd sound		Systolic murmur	3rd sound	Left auricle enlarged in oblique views	Systolic expansion, left auricle: Anterior view	Systolic expansion, left auricle: Oblique views	Left ventricle	Axis	Ventricular preponderance	Rhythm	Ventricular extrasystoles
1	M	50	40	+	0	P	0	−	Long	0	0	160/100	FS	0	++	+	+	+	L	LV+	N	+
2†	M	54	5	0	+	HF	+	0	Long	+	+	145/95	FS	+	++	+	+	+	L	LV+	N	0
3†	M	75	36	0	0	HF	+	+	Long	+	++	130/75	−	−	+	−	−	−	R	R.BBB	AF	0
4	M	52	2	0	0	P	0	+	Late	0	0	160/80	FS ML	0	0	+	−	+	N	0	N	0
5†	M	68	35	0	0	P	+	++	Late	+	+	125/80	FS ML	+	+	−	−	+	L	LV+	AF	++
6	M	63	2	0	0	P	D	+	Long	+	0	140/70	FS	0	+	++	++	+	L	LV++	N	+
7	M	50	36	0	0	P	D	+	Long	+	++	150/85	FS	++	++	++	++	+	N	?LV+	AF	+
8	M	35	10	0	0	P	0	0	Long C	+	+	110/60	FS ML	+	+	+	++	0	N	0	N	0
9	M	25	15	+	0	P	0	0	Long C	+	++	160/80	FS ML	++	0	+	++	+	N	0	N	0
10	M	36	24	+	+	SBE	0	+	Long	+	0	125/70	FS ML	+	0	+	++	+	N	0	N	0
11	M	55	2	0	0	P	0	+	Long	+	+	130/80	FS	++	+	++	+	+	N	0	AF	+
12†	M	55	9	0	0	P	+	−	Long	+	+	155/75	FS	++	++	−	−	+	N	?LV+	AF	++
13†	M	52	8	0	0	P	+	−	Long	+	−	115/80	−	−	+	−	−	+	N	LV++	N	+
14	M	61	35	0	0	P	0	+	Long C	+	0	150/80	FS	0	+	++	+	+	L	LV+	N	++
15†	M	56	2/12	0	+	HF	+	−	Long	0	+	110/75	FS	+	+	++	++	+	N	0	N	0
16	F	57	41	0	+	SBE	0	0	Long C	0	0	150/90	FS ML	0	+	+	+	0	N	0	N	+
17	F	52	30	0	+	P.SBE	0	+	Long	+	0	130/80	FS	0	+	++	++	+	N	LV++	N	+
18	F	36	24	+	0	D	D	+	Late	+	0	150/70	FS ML	+	+	++	−	+	L	0	N	0
19	M	60	4	+	0	P	0	+	Long	0	0	140/90	FS ML	0	+	+	+	+	L	0	N	0
20	M	54	32	0	0	P	0	0	Long C	0	0	160/80	FS ML	0	+	+	++	+	N	LV++	N	0
21†	F	23	9/12	+	+	HF	+	+	Long	+	++	110/60	−	−	+	+	++	−	N	?LV+	N	+
22	M	24	17	0	+	SBE	0	−	Long	+	++	120/65	FS	+	+	+	+	+	N	LV+	N	0
23	F	49	28	+	+	SBE	0	+	Long	0	+	125/80	FS	+	+	+	+	0	L	LV+	N	0
24	M	59	35	0	0	P	0	+	Long	0	+	160/80	FS ML	+	+	+	+	+	N	?LV+	AF	0
25	M	67	1	0	0	0	0	+	Long	0	0	145/85	FS	+	+	++	+	0	N	?LV+	N	0
26	M	65	34	0	0	0	0	+	Late	0	0	160/100	FS ML	+	+	+	+	+	L	LV+	N	+
27	M	58	7	0	+	SBE	0	0	Long C	0	0	150/90	FS	0	+	0	+	+	N	LV+	N	0
28	M	65	5	0	0	HF	+	+	Long C	+	+	120/85	FS ML	+	+	+	+	+	N	0	AF	0
29†	M	58	35	0	0	HF	+	+	Long	+	+	150/105	FS	+	++	++	++	++	L	LV+	AF	0
30†	M	63	37	0	+	SBE	0	0	Long	+	0	130/80	FS	0	0	−	−	+	L	0	N	0

† = necropsy
P = palpitation
HF = heart failure
BE = bacterial endocarditis

D = dyspnœa
C = crescendo in late systole
ML = maximal vibrations in late systole

FS = fills systole
N = normal
L = left axis deviation
R = right axis deviation
AF = auricular fibrillation

− = unrecorded

* = clinical estimation of left ventricular hypertrophy

backwards in systole (Lenègre *et al.*, 1942). Occasionally systolic uncoiling of the aorta causes a movement of the œsophagus posteriorly and upwards but this can be related to excessive movement of the aorta when viewed in the left oblique position. These movements of the normal left auricle are slight when related to the degree of activity of the whole heart.

Systolic expansion of the left auricle was appreciated as a clinical sign in a case described by Owen and Fenton (1901) where systolic pulsation of the right side of the chest was due to massive enlargement of the left auricle. Necropsy showed a grossly dilated mitral valve ring. In the same year Holzknecht, referring to the radiological appearance of the left border of the heart, said that " under pathological circumstances one sees not uncommonly an obvious middle prominence with arterial pulsation . . . one should remember mitral incompetence which produces positive pulsation of the left auricle." In an early textbook of cardiac radiology, Schwarz (1911) noted systolic filling of the left auricular appendix in mitral valve disease. Bedford (1927) observed on radioscopy that there was vigorous systolic pulsation of the left auricle from mitral reflux in two cases of mitral valve disease. Rapid serial full size X-ray films were used by Chamberlain and Dock (1927) to show sudden dilatation in early systole of the left atrium on the left border of the heart in a patient with mitral incompetence which was confirmed at necropsy. In the same year Mahaim (1927) observed paradoxical pulsation of the right and left auricles on the right border of the heart, and thought that this movement was due to thinning of the muscle wall of the left auricle and was occurring in auricular systole. With the introduction of roentgenkymography, Stumpf (1936) recorded systolic bulging of the

left auricular zone on the left border of the heart in about one-third of cases of mitral valve disease: he did not think that this indicated mitral incompetence in view of the proximity of the conus arteriosus and great vessels which normally move outwards in systole. Lemke (1939) disagreed with Stumpf; he showed by roentgenkymography systolic expansion of the left atrium on the right border of the heart in the anterior view in three cases, and attributed it to mitral incompetence. The same conclusion was reached by Gubner *et al.* (1939), Laubry *et al.* (1939), and Routier and Heim de Balsac (1942). Lenègre *et al.* (1942) examined 600 patients by fluoroscopy for pulsation in the oblique views: of 69 cases of mitral valve disease 51 had abnormal left auricular pulsation. In the right oblique position a barium swallow showed that the posterior border of the heart from the pulmonary artery (or left bronchus) impression almost to the diaphragm moved backwards in systole. In the left oblique position the same movement was seen, usually less clearly, and could be contrasted with forward movement of the left ventricle. They accepted this "systolic retropulsion" of the left auricle as evidence of mitral incompetence although it sometimes occurred in mitral stenosis with no systolic murmur. They did not consider systolic expansion of the left auricle in the anterior view because they assumed that it could only be seen on the right border of the heart when there was aneurysmal dilatation of the left auricle. By means of roentgenkymography (Heim de Balsac and Pannier, 1945; Routier *et al.*, 1950), and by electrokymography (Luisada and Fleischner, 1948; Lian *et al.*, 1948; McKinnon and Friedman, 1950; Soulié *et al.*, 1950) systolic expansion of the left auricle has been demonstrated, usually in the oblique views, in almost all cases of mitral valve disease even in the absence of a systolic murmur. The findings of auscultation and of radiology have been so much at variance that Froment *et al.* (1950) have denied that systolic expansion of the left auricle is a sign of mitral incompetence. They quoted one case; this patient showed systolic expansion although subsequent necropsy revealed a stenosed mitral valve which was competent to their water test (Froment *et al.*, 1945). They postulate that systolic expansion of the left auricle is due to displacement of blood when the fibrotic mitral valve and ring is forced like a piston deep into the left auricle. Standard textbooks of cardiac radiology tend to support the view that systolic expansion of the left auricle is one of the signs of mitral incompetence (Roesler, 1943; Schwedel, 1946; Zdansky, 1949). Systolic expansion of the left auricle following a rupture of chordæ tendineæ has been seen radiologically by Bailey and Hickham (1944), and at operation by Brock (1950). Heim de Balsac and Pannier (1945) noted that it was less likely to be seen when the left auricle was greatly dilated.

FIG. 8. — Anterior view of Case 6 showing enlargement and systolic expansion of the left auricle. The arrows indicate the direction of pulsation in ventricular systole.

FIG. 9.—Angiocardiogram of Case 6 showing enlargement of the left auricle. The enlarged left ventricle is seen below the left auricular bulge.

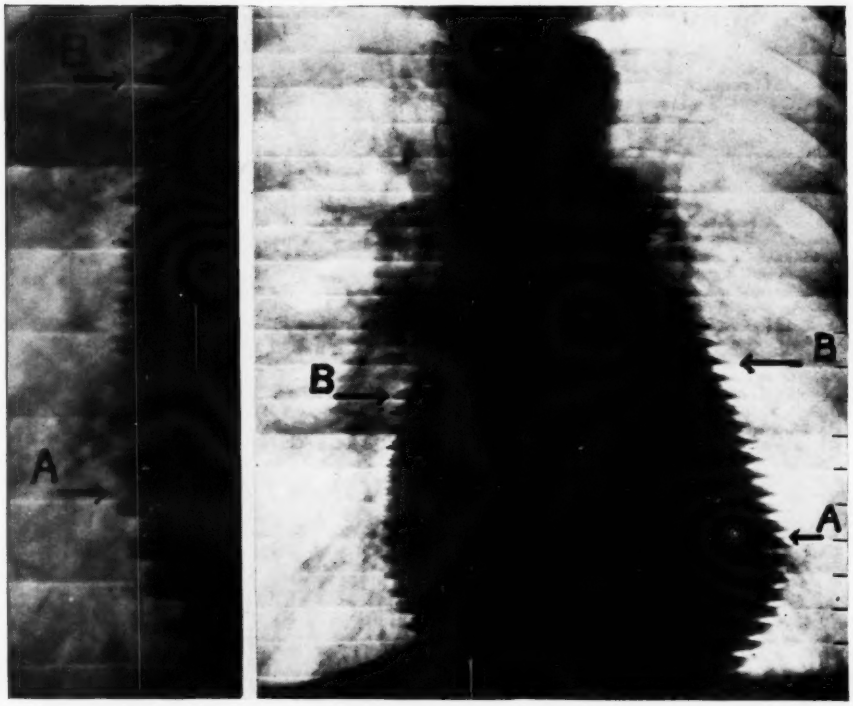
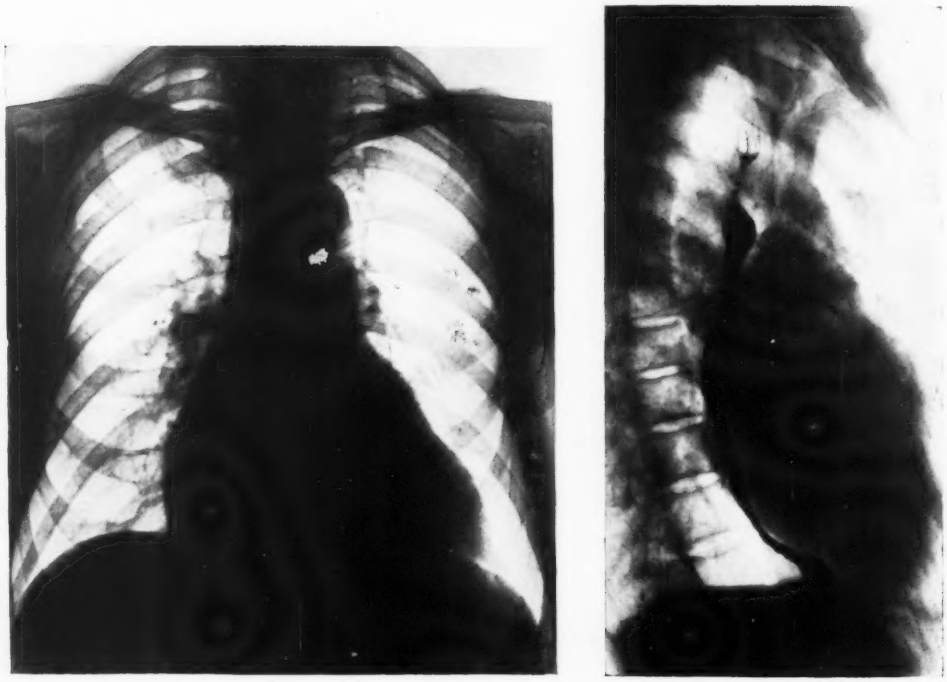


FIG. 10.—Kymogram of Case 6. The systolic inward movement of the left ventricle (A) may be contrasted with the simultaneous outward movement of the left auricle (B). An enlargement of the right border shows the paradoxical movement of the right (A) and left (B) auricles.

Systolic expansion of the left auricle was found in 25 of our 30 patients on fluoroscopy, including four who came to necropsy. The remaining 5 patients died without being examined for this sign. We have not been concerned with slight pulsation or with that which could only be found by kymography because such pulsation occurs in many cases of predominant stenosis. In the anterior view the left auricle expanded laterally in systole appearing as a momentary local bulge high up on the left border, and as a less obvious bulge in the upper part of the right border (Fig. 8, 9 and 10); the lower part of the right border, the right auricle, was seen to move in the opposite direction, i.e. inwards in systole. Sometimes a paradoxical movement of the left auricle could be seen through the right auricular shadow (Fig. 8 and 9). In the oblique views the barium-filled œsophagus was moved backwards by the left auricle during ventricular systole. This backward movement of the left auricle, best seen in full inspiration (Lenègre *et al.*, 1942) is not a sign of mitral incompetence for it is present in many cases of pure mitral stenosis. In our patients the left auricular movement was usually of greater degree than in mitral stenosis and was out of proportion to the degree of activity of the rest of the heart; it was always visible in the anterior view. In fact, we do not use the term systolic expansion without seeing this movement both in the anterior and oblique views, and believe that this condition must be satisfied to make a firm radiological diagnosis of mitral incompetence. Absence of systolic expansion, however, cannot be taken to mean that there is no regurgitation as has been emphasized by Heim de Balsac and Pannier (1945).

Enlargement of the left auricle was found in 26 of our 30 cases (Fig. 9 and 11); it varied from slight to moderate and it was never aneurysmal as in some cases of combined mitral stenosis and



A B

FIG. 11.—(A) Anterior view of Case 5 showing the convex left auricular bulge on the left border of the heart, and enlargement of the left ventricle. (B) Right oblique view of Case 6 showing moderate enlargement of the left auricle posteriorly.

mitral incompetence. The remaining four patients showed no enlargement though systolic expansion was clear. Kuttner and Markowitz (1948) considered that a diagnosis of mitral incompetence was justified in children even in the absence of enlargement. In two cases the enlarged left auricle was seen posterior to the barium-filled œsophagus. Enlargement of the left ventricle in mitral incompetence has been described by many authors (Steel, 1929; Stumpf, 1936; Roesler, 1943; Zdansky, 1949), and we confirmed this in 24 of our 30 cases (Fig. 11A). In four patients there was increased pulsation of the hilar vessels, possibly the veins and, if so, comparable to the jugular pulse in tricuspid incompetence, a feature noted by Schwarz (1911) and recently by Routier and Heim de Balsac (1942).

ELECTROCARDIOGRAPHY

The electrocardiogram confirmed that there was auricular fibrillation in eight patients and sinus rhythm in the remainder. Multiple ventricular extrasystoles were recorded in twelve patients, the ectopic focus being in either ventricle. The P waves were always normal, none showing the large bifid waves characteristic of mitral stenosis. Left axis deviation was present in one-third of the cases and right axis deviation was never seen. Berliner and Master (1938) noted the shift towards left ventricular preponderance in pure mitral incompetence. Half our patients showed abnormal QRS–T changes indicating left ventricular hypertrophy (Fig. 12). These changes were not so great either in voltage increase or S–T deviation as in aortic valve disease or hypertensive heart disease.

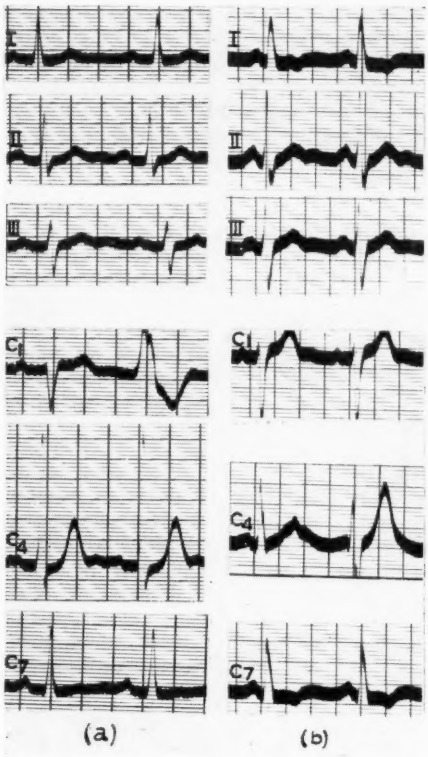


FIG. 12.—(a) Electrocardiographic evidence of some left ventricular hypertrophy in Case 14. One ventricular extrasystole is seen. (b) Electrocardiographic evidence of moderate left ventricular hypertrophy in Case 6. One ventricular extrasystole is seen.

No patient showed cardiographic evidence of right ventricular hypertrophy, though in one case in which the diagnosis of mitral incompetence was confirmed at necropsy there was right bundle branch block. These cardiographic findings contrast with those in mitral stenosis where extrasystoles tend to be auricular, P waves abnormal, left axis deviation rare, and the QRS–T abnormal in right chest leads rather than in those from the left side.

NECROPSY FINDINGS

Confirmation of the clinical diagnosis of pure mitral incompetence was obtained in the nine patients who came to necropsy. Eight died of congestive heart failure and all of these had moderate increase in heart weight which was mainly due to hypertrophy of the left ventricle though these showed slight hypertrophy of the right ventricle also. The left auricle was moderately dilated but was never aneurysmal and the posterior wall above the mitral valve frequently (4 of 9) showed an area of pathological endocardium—the " MacCallum patch " (Fig. 13). We think that this is the effect of the regurgitant jet rather than the direct result of the rheumatic endocarditis. One patient died of coronary embolism without antecedent heart failure (Case 30) and showed moderate

left ventricular hypertrophy with no abnormality of the right ventricle. The mitral orifice was of normal size in one case and dilated in the remainder (Fig. 14). All showed thickening and deformity of the valve cusps with some calcification in two. The chordæ tendineæ were thickened in six and in two of these a chorda was ruptured (Fig. 15). Histological evidence of active rheumatism with Aschoff nodules was found in only one patient, the youngest in the series (Case 21). All the remainder showed varying degrees of scar tissue formation which might be regarded by some histologists as the legacy of past rheumatism though there was no certain evidence of this.

Summary and Conclusions

Thirty patients believed to have pure organic mitral incompetence have been investigated. The diagnosis was confirmed at necropsy in 9, in whom the clinical features were the same as in the remaining 21.

The natural history of pure organic mitral incompetence is longer and more benign than that of mitral stenosis, except that it is not infrequently interrupted by bacterial endocarditis. The ætiology may be different from that of mitral stenosis in view of its preponderance in the male sex and the rarity of a history of any form of rheumatic fever. Histological evidence of rheumatic carditis is difficult to find; yet this apparent ætiological difference may only lie in the degree of rheumatic reaction. In these general respects there are similarities with isolated aortic stenosis where males preponderate, a history of rheumatic fever is rare, and the natural course is long.

Patients with organic mitral incompetence are free of significant symptoms except in the few with heart failure, but the complaint of palpitation due to multiple ventricular extrasystoles is fairly common. The frequency of bacterial endocarditis in the course of mitral incompetence is an indication for penicillin prophylaxis in all cases undergoing surgical or dental treatment. Heart failure, though late in appearance, tends to be rapidly progressive.

There is no clinical evidence of right ventricular hypertrophy or severe pulmonary hypertension in pure mitral incompetence, and palpation frequently indicates left ventricular enlargement which may be confirmed electrocardiographically and radiologically. The loud apical murmur always fills systole and is often maximal in late systole; it extends up to, and usually embraces, the second sound; occasionally the early vibrations are small when the murmur appears to be confined to late systole on auscultation. Splitting of the second sound in the pulmonary area was wider than normal in some cases and in these the systolic murmur extended to the earlier aortic component but not to the later pulmonary component. The length of the systolic murmur, its position in systole and relationship to the sounds are as important as loudness. The systolic murmur in aortic stenosis may be loud at the mitral area but is well heard at the aortic area and is loudest in mid-systole, finishing before the second sound. The absence of a loud first sound and particularly of the opening snap in patients with mitral incompetence emphasizes the fact that these signs are related to mitral stenosis. The finding of a soft mid-diastolic murmur in one necropsy case of pure mitral incompetence means that this sign does not always indicate stenosis. The third heart sound was frequently present in these cases of mitral incompetence, which is in contrast with its rarity in pure mitral stenosis.

The most important radiological sign of mitral incompetence is obvious systolic expansion of the left auricle which should be seen in both the anterior and oblique views, especially the former. It is important that a slight degree of systolic backward movement in the right oblique view should not be taken to indicate mitral incompetence as it occurs in predominant stenosis, and conversely the absence of auricular systolic expansion does not exclude mitral incompetence if the other physical signs suggest this diagnosis.

Pure mitral incompetence has characteristic physical signs and radiological features. It is clear that this is an uncommon disease: it should never be diagnosed loosely on hearing an apical systolic murmur, but only after due consideration of the special characteristics of the murmur, the other physical signs, and radiological features. The differential diagnosis between pure mitral stenosis

and pure mitral incompetence is summarized in Table I. The presence of the signs that we have described when combined with those of mitral stenosis or other valve lesions help in the assessment of the degree of associated mitral incompetence.

We are grateful to Dr. Evan Bedford, Dr. Graham Hayward and Professor McMichael for permission to study Cases 13, 17, 18, 27, 29, and 30, and to Professor Dorothy Russell, Dr. Doniach, and Dr. Hudson for the morbid anatomical findings, and Dr. F. G. Wood for the roentgenkymograms.

It is a pleasure to thank Sir John Parkinson and Dr. William Evans for much helpful advice and criticism.

FIG. 13.—The mitral valve and MacCallum patch in Case 21.

SUMMARY OF THE NINE NECROPSY CASES

Case 2, man, aged 56. Heart weight 620 g. (body weight 60 kg.). No stenosis of mitral valve which easily admitted three fingers (Fig. 14). Both cusps puckered and thickened at contact margins. Chordæ thickened, and group of three or four from anterior cusp torn and free end covered with blood clot (Fig. 15). Other valve cusps normal; pulmonary valve ring 8·5 cm. Left ventricle dilated and hypertrophied (1·5 cm.) (Fig. 15). Right ventricle dilated and hypertrophied (0·7 cm.). Moderate dilatation of left auricle with some hypertrophy; endocardium thickened and wrinkled over posterior wall above the valve ring.

Microscopy of left auricular endocardium near valve ring showed thickening of fibrinoid tissue and infiltration by round cells and occasional plasma cells. Fibrinoid degeneration of small arteries. Left ventricular myocardium near valve ring also showed fibrinoid replacement of muscle cells and scattered small foci of round cells near arteries. No Aschoff nodes seen in any section.

Comment. No definite histological evidence of rheumatic carditis but changes suggestive of quiescenl chronic rheumatism. Death due to heart failure and bronchopneumonia.

Case 3, man, aged 75. Heart weight 560 g. (body weight 52 kg.). No stenosis of mitral valve (12·5 cm. circumference). Fibrous thickening with puckering throughout free margins of mitral cusps, calcification in posterior cusp. Slight thickening and no shortening of chordæ tendineæ. Aortic, tricuspid, pulmonary valves normal. Great dilatation of left auricle. Considerable hypertrophy and dilatation of left ventricle, moderate of right ventricle and right auricle.

Fig. 14.—Dilated and thickened mitral valve ring (easily admitting three fingers) in Case 2 viewed from the left auricle.

Microscopy of anterior cusp of mitral valve showed hyaline areas, no cells except scanty spindle fibroblasts. Posterior cusp similar except scanty deposits of fibrin occupying margin of cusp and slight calcification near attachment. Both cusps entirely avascular. Aortic and tricuspid valves normal Left and right ventricles hypertrophy of muscle-fibres and occasional foci of subendocardial fibrosis. Conspicuous hypertrophy of muscle of left auricle. Separation of fibres by diffuse fibrosis in places.

Comment. There was no definite histological evidence of rheumatic carditis in this case although the macroscopic appearances were suggestive of this condition.

Case 5, man, aged 68. Heart weight 604 g. (body weight 62·3 kg.). No stenosis of mitral valve, orifice 14 cm. in circumference. Fibrous thickening and puckering of posterior cusp and half anterior cusp. Slight thickening without shortening of some chordæ tendineæ. Aortic and other valves normal. Zone of irregular, fibrous thickening of endocardium of left auricle immediately above posterior cusp of mitral valve, and similar patch above anterior cusp. Considerable hypertrophy and dilatation of left ventricle (1·4 cm. thick), and of right ventricle. Great dilatation and very slight hypertrophy of left auricle. Considerable dilatation and hypertrophy of right auricle.

Microscopy of posterior cusp showed thickening by elastic and collagen fibres, without inflammatory infiltration. Cells restricted to a small number of spindle fibroblasts. Similar thickening affected peripheral part of anterior cusp of mitral valve.

Comment. As in Case 3, to which this bears a strong resemblance, there was no histological evidence in support of a rheumatic basis for the mitral lesion. Alternatively the fibrous thickening of the cusps may have been built up by the organization of thrombotic incrustations.

Case 12, man, aged 55. Heart very large. Dilatation of the left auricle, slight hypertrophy of the right ventricle and great hypertrophy of the left ventricle. Gross deformity and thickening of the mitral valve cusps with no stenosis. Other valves normal.

Case 13, man, aged 52. Heart weight 620 g. (body weight 56 kg.). Left ventricle moderately hypertrophied, and left auricle greatly dilated. Right ventricle dilated and slightly hypertrophied. Aortic, pulmonary, and tricuspid valves normal, Mitral valve widely patent (16·5 cm. circumference) with cusps grossly thickened

FIG. 15.—Thickened and ruptured chordæ tendineæ in Case 2. Left ventricular hypertrophy.

but not fused. Valve ring contained calcareous deposits which extended into posterior cusps. Microscopical examination of posterior mitral cusp and neighbouring tissue showed left auricular endocardium grossly thickened by irregular scar tissue and elastosis. Mitral ring vascular and enlarged by fibrosis and calcareous deposits, and among the vessels there were thick walled, muscular arterioles. Mitral cusps thickened by fibrosis.

Comment. This patient died within one year of the onset of heart failure. There were scars of past rheumatism.

Case 15, man, aged 56. Heart weight 518 g. (body weight 50 kg.). No mitral stenosis: very slight thickening of posterior cusp of mitral valve; fibrous vegetation (3 × 1·4 × 1 cm.) firmly adherent to anterior cusp; ulceration of lower 1·5 cm. of this cusp, with small friable vegetations on its surface; fusion, thickening and ulceration of attached chordæ tendineæ. Pinkish-grey granular thickening (5 × 3·5 cm.) over posterior wall of left auricle extending upwards from mitral valve. Other valves normal. Moderate hypertrophy without dilatation of left ventricle. Slight hypertrophy and moderate dilatation of right ventricle. Moderate dilatation and hypertrophy of left auricle, and slight of right auricle. Histological changes confined to anterior cusp of mitral valve and posterior wall of left auricle. Mitral cusp showed a thrombotic vegetation containing infected focus. Valve cusp greatly thickened by vascularized fibrous tissue and infiltrated by numerous large mononuclear cells, a few multinucleate giant cells of rheumatic type, and scantier lymphocytes. Proximal part of cusp normal. Endocardium of posterior wall of left auricle unevenly coated with a thin layer of fibrin.

Comment. The presence of preceding rheumatic endocarditis was suggested by the fusion and shortening of the chordæ tendineæ but no definite histological evidence of rheumatic carditis could be found. Bacterial endocarditis caused great injury to anterior cusp of mitral valve, resulting in extreme mitral incompetence and heart failure.

Case 21, woman, aged 23. Heart weight 434 g. (body weight 39 kg.). No mitral stenosis. Thickening (up to 0·3 cm.) of both cusps of mitral valve (10·9 cm. circumference). Succulent grey thickening of free border of anterior cusp, with granulations of similar tissue at attachments of chordæ (Fig. 13). Calcification and rupture of chordæ of this cusp except for one group at posterior commissure. A few coarse grey

rheumatic vegetations fixed to auricular side of attachments of chordæ tendineæ to posterior cusp. Calcified thrombus adherent to a few of these chordæ, three being ruptured. Area (5 × 2·7 cm.) of confluent grey tough vegetations in endocardium of left auricle above posterior cusp of mitral valve (Fig. 13). Remaining valves normal. Considerable hypertrophy of left ventricle; very slight of right ventricle. Hypertrophy and dilatation of left auricle. On microscopical examination abundant evidence of active rheumatic carditis affecting both cusps of mitral valve and occasional Aschoff nodes both in interventricular septum and walls of both ventricles. Fibrin vegetations on anterior cusp of the mitral valve, no organisms seen.

Comment. Histological evidence of both old and active rheumatic carditis was plentiful in this case and formed the background of a superimposed bacterial endocarditis. The latter, however, appeared to have been subdued by the use of antibiotics, as judged by the appearances of the vegetations and the spleen, though the rheumatic inflammatory process was unabated.

Case 29, man, aged 58. Heart weight 640 g. (body weight 50 kg.). Moderate left ventricular hypertrophy and great dilatation of left auricle. Right ventricle slightly hypertrophied. Mitral valve easily admitted three fingers and thickening of anterior cusp. Chordæ thickened. Other valves normal. On microscopical examination no evidence of old or recent rheumatism.

Comment. This is an example of long standing mitral valve disease without stenosis, associated with great enlargement of the left auricle, which showed systolic expansion. Mild hypertension was possibly a contributory factor but in view of the history and necropsy findings was not the primary cause of mitral incompetence.

Case 30, man, aged 63. Extensive anterior cardiac infarction was found to be due to a septic embolus (streptococcus fæcalis), with a mycotic aneurysm in the descending branch of the left coronary artery. Heart weight 510 g. (body weight 69 kg.). Slight hypertrophy of left ventricle, none of right. Mitral valve showed no stenosis and cusps thickened, bearing numerous smooth rubbery vegetations. Microscopical examination showed organisms in vegetations, and fibrous thickening of mitral valve cusps in other areas. No definite evidence of present or past rheumatism. Other valves normal.

Comment. The mitral incompetence in this patient was slight, but it resulted in bacterial endocarditis which proved fatal from coronary embolism.

References

Alzamora-Castro, V., Rubio Watkins, C., and Battilana, G. D. (1947). *Rev. argent. Cardiol.*, **15**, 25.
Bailey, O. T., and Hickham, J. B. (1944). *Amer. Heart J.*, **28**, 578.
Baker, L. A., and Musgrave, D. (1947). *Ann. intern. Med.*, **26**, 901.
Bedford, D. E. (1927). *Amer. Heart J.*, **3**, 127.
—— (1945). Personal communication.
Berliner, K., and Master, A. M. (1938). *Arch. intern. Med.*, **61**, 39.
Brock, R. C. (1950). *Guy's Hosp. Rep.*, **99**, 236.
Cabot, R. C. (1926). *Facts on the Heart.* Saunders, Philadelphia.
Cates, J. E., and Christie, R. V. (1951). *Quart. J. Med.*, **20**. 93.
Chamberlain, W. E., and Dock, W. (1927). *Ann. intern. Med.*, **40**, 521.
Cossio, P., and Berconsky, I. (1943). *Rev. Argent. Cardiol.*, **7**, 199.
Corvisart, J. N (1813). *A Treatise on the Diseases and Organic Lesions of the Heart and Great Vessels.* Translation by C. H. Webb, London.
Evans, W. (1948). *Cardiology.* Butterworth, London.
Fishberg, A. M. (1940). *Heart Failure.* 2nd ed., Lea and Febiger, Philadelphia.
Freeman, A. R., and Levine, S. A. (1933). *Ann intern. Med.*, **6**, 1371.
Froment, R., Gonin, A., and Gallavardin, L. (1950). *Arch. Mal. Coeur.*, **8**, 678.
——, Guinet, Coblentz, and Gallavardin, L. (1945). *Arch. Mal. Coeur.*, **38**, 206.
Gee, S. (1893). *Auscultation and Percussion.* 4th ed., Smith, Elder and Co., London.
Gubner, R., Crawford, J. H., Smith, W. A., and Ungerleider, H. E. (1939). *Amer. Heart J.*, **18**, 729.
Heim de Balsac, R., and Pannier, R., (1945). *Rev. belge Sci. med.*, **16**, 1.
Hirsch, S., and Gubner, R. (1936). *Amer. Heart J.*, **12**, 413.
Holzknecht, G. (1901). *Archiv. und Atlas der normalen und pathologischen Anatomie.* Lucas, Graefe, and Sillem, Hamburg.
Hope, J. (1849). *A Treatise on Diseases of the Heart.* 4th ed., Churchill, London.
Karsner, H. T., and Koletsky, S. (1947). *Calcific Disease of the Aortic Valve.* J. B. Lippincott Co., Philadelphia.
Kumpe, C. W., and Bean, W. B. (1948). *Medicine*, **27**, 139.
Kuttner and Markowitz (1948). *Amer. Heart J.*, **35**, 718.
Laennec, R. T. H. (1829). *A Treatise on the Diseases of the Chest and on Mediate Ausculation.* Translation by J. Forbes, London.
Laubry, C., Cottenot, P., Routier, D., and Heim de Balsac, R. (1939). *Radiologie Clinique du Coeur et des Gros Vaisseaux.* Masson et Cie., Paris.
Leatham, A. (1949). *Postgrad. med. J.*, **25**, 568.
—— (1951). *Brit. Heart J.*, **13**, 153.
Lemke, H. H. (1939). *Fortschritte auf dem Gebiete der Roentgenstrahlen*, **59**, 372.
Lenègre, J., Mathivat, A., and Philippe, L. (1942). *Arch. Mal. Coeur.*, **35**, 171.

Lewis, Sir Thomas (1933). *Diseases of the Heart.* MacMillan, London.
Lian, C., Facquet, J., and Minot, G. (1948). *Arch. Mal. Coeur.*, **41**, 727.
Luisada, A. A., and Fleischner, F. G. (1948). *Amer. J. Med.*, **4**, 791.
Mackenzie, Sir James (1916). *Principles of Diagnosis and Treatment of Heart Affections.* 2nd impression, Oxford Medical Publications, London.
Mahaim, I. (1927). *Schweiz. med. Wschr.*, **57**, 183.
McKinnon, J. B., and Friedman, B. (1950). *Circulation*, **2**, 572.
Master, A. M. (1948). *Arch. intern. Med.*, **81**, 518.
Miller, J. H., and Wedum, B. G. (1949). *Amer. J. Dis. Child.*, **78**, 703.
Owen, I., and Fenton, W. J. (1901). *Clinical Society Trans.*, **34**, 183.
Parkinson, J. (1945). The Harveian Oration. *Lancet*, **2**, 657.
Potain, C. (1894). *Clinique Medicale de la Charité.*
Rappaport, M. B., and Sprague, H. B. (1942). *Amer. Heart J.*, **23**, 591.
Roesler, H. (1943). *Clinical Roentgenology of the Cardiovascular System.* 2nd. ed., Thomas, Illinois.
Routier, D., and Heim de Balsac, R. (1942). *Arch. Mal. Coeur.*, **35**, 73.
——, ——, and Alessandris, L. (1950). *Sem. Hôp. Paris*, **26**, 60.
Schwarz, G. (1911). *Die Rontgenuntersuchung des Herzens und der grossen Gefässe.* 5th ed., Leipzig and Vienna.
Schwedel, J. B. (1946). *Clinical Roentgenology of the Heart.* Hoeber, New York.
Soulié, P., Di Mattes, J., and Marchal, M. (1950). *Arch. Mal. Coeur.*, **43**, 14.
Sprague, H. B. (1930). *J. Amer. med. Ass.*, **94**, 1037.
——, and White, P. D. (1926). *Amer. Heart J.*, **1**, 629.
Steel, D. (1929). *Amer. J. Roentgenol*, **21**, 220.
Steell, G. (1906). *Text Book on Diseases of the Heart.* Manchester University Press.
Stumpf, P. (1936). *Roentgenkymographische Bewegungslehre innerer Organe.* Thieme, Leipzig.
Weiss, O., and Joachim, G. (1911). *Z. Klin. Med.*, **73**, 239.
White, P. D. (1947). *Heart Disease.* 3rd ed., MacMillan, New York.
Wiggers, C. J. (1923). *Modern Aspects of the Circulation in Health and Disease.* Lea and Febiger, New York.
——, and Feil H. (1921). *Heart*, **9**, 149.
Wood, P. (1950). *Proc. R. Soc. Med.*, **43**, 195.
Zdansky, E. (1949). *Roentgendiagnostik des Herzens und der grossen Gefasse.* 2nd ed., Vienna.

THE ELECTROCARDIOGRAM DURING ANGIOCARDIOGRAPHY

BY

GEOFFREY REYNOLDS

From the Cardiac Department, Guy's Hospital

Received June 24, 1952

It is often said that angiocardiography carries little risk, and series of more than a thousand injections without a death are on record (Sussman, 1948; Horger *et al.*, 1951). During recent years, however, more than thirty deaths have been reported—the majority in children with cyanotic congenital heart disease. The exact cause of these deaths has still to be discovered.

When Mr. R. C. Brock began the surgical treatment of congenital heart disease at Guy's Hospital in 1947, it was found that angiocardiography formed an important part of the preliminary investigation of the patients. The risk of the procedure was soon confirmed and there were three deaths; the first two were reported by Campbell and Hills (1950), and all three (with the first of those described here) by Carnegie (1951). It was decided then to take electrocardiograms during the investigation in the hope of discovering the cause of such deaths and of providing a warning of impending trouble that might help to prevent them.

This paper analyses the first 75 consecutive electrocardiograms, taken on 73 patients, one of whom died. Records of two later patients who died are also described. 72 of these 75 patients had congenital heart lesions, the majority Fallot's tetralogy; all but 4 were cyanosed. Their ages ranged from 3 to 35 years.

The technique of the investigation used here has been described in detail by Carnegie (1951). General anæsthesia was given for 58 of the angiocardiographies, including all but two where the patient was under 14 years. Patients in the second half of the series received quinidine, 3–10 mg. by mouth, before the investigation, and procaine, 2–3 mg. per kilogram of body weight intravenously, during it in addition to routine premedication with sedatives. Diodone was the opaque medium used in every case, about 1·2 ml. of a 70 per cent solution per kilogram of body weight being injected into a peripheral vein.

The three standard electrocardiographic leads were taken before the injection, continuously for the first two or three minutes after it, and then intermittently as indicated.

Electrocardiographic Changes

The heart rate was usually between 100 and 150 a minute at the time of injection of the diodone. Characteristic changes followed this in 59 of the 75 cases—an initial slowing lasting twenty to thirty seconds, which may have been due to a direct effect of the diodone on the heart (Gordon *et al.*, 1950), followed by an increase lasting for the next minute or two, and then a steady fall unless restlessness due to returning consciousness caused it to rise again.

Seventy-eight changes that were thought to be significant were recorded in 45 (60%) of the 75 electrocardiograms in the series. These were divided into three groups: those that seemed to be due to injection of the diodone; those due to other factors concerned in the investigation, particularly the anæsthetic; and those probably not due to the procedure at all as they had been seen at other times (Table I). This grouping could, of course, only be approximate and there is

no doubt that some of the changes that appeared to be due to the diodone may have been due to other causes and *vice versa*.

Changes were significantly more frequent among patients who were under anæsthesia (69%) than among those who were not (41%).* This was largely due to changes that were thought, from the time they occurred, to be due directly to the anæsthetic.

Changes thought to be due to the diodone alone were also a little more frequent among patients under anæsthesia (52%) than among those who were conscious (41%); more frequent among the younger (59%) than among the older patients (39%); and significantly more frequent among those whose disability was above average (65%) than among those in whom it was below this (35%).*

TABLE I

ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING 75 ANGIOCARDIOGRAPHIES

	Due wholly to diodone	Due partly to diodone	Due to other factors	Occurring normally	Total
Extrasystoles	4	1	2	1	8
Paroxysmal tachycardia	2	0	0	0	2
Changing pacemaker	3	2	5	5	15
Latent A-V block	10	1	1	0	12
Partial A-V block	3	0	0	0	3
Bundle branch block	6	3	2	0	11
S–T segment depression	12	2	3	0	17
S–T depression and/or elevation	5	3	2	0	10
Total	45	12 (57)	15	6	78
Number of patients	29	11 (36)	10	5	45

The last was the most striking difference but was only present among the older patients (Table II). No significant factor was found among patients under ten years of age. There was no significant correlation between these changes and the degree of the patient's cyanosis.

TABLE II

PERCENTAGES OF PATIENTS SHOWING ELECTROCARDIOGRAPHIC CHANGES DUE TO DIODONE DIVIDED BY AGE AND BY DEGREE OF DISABILITY

Age	*Disability*	
	below average	*above average*
0–9 years	56% (16)	64% (22)†
10 years and above	15% (20)	69% (16)*

Numbers of cases in each group are shown in brackets.

† Difference 8 per cent. Twice its standard error 32 per cent.
* Difference 54 per cent. Twice its standard error 28 per cent.

Ectopic Arrhythmias. Extrasystoles were recorded in only 8 cases; in 7 they were ventricular.

Paroxysmal ventricular tachycardia occurred as one of the multiple abnormalities that preceded ventricular fibrillation in the boy who died. Otherwise paroxysmal tachycardia occurred only once. This was in a patient who had no anæsthetic, and a nodal tachycardia appeared about three minutes after the diodone had been injected and lasted seven seconds.

No instance of auricular flutter or fibrillation was seen, but both flutter and fibrillation of the ventricle were recorded over a period of more than two hours in the boy who died.

* Difference more than twice its standard error.

A change of pacemaker occurred in 15 cases.

In all, these arrhythmias were present in 18 cases. They were usually first seen before the injection of diodone. In six of them similar changes had been seen at other times; in seven they appeared to be wholly and in one partly due to the anæsthetic; and in two they seemed to be wholly and in three partly due to the diodone. In five cases such arrhythmias, present before the injection, disappeared a few seconds after it. They occurred less frequently in the patients given quinidine and intravenous procaine.

It is, thus, unusual for diodone to cause these arrhythmias, and it is as likely to stop them.

These findings contrast with those during angiocardiography where the injection is made through a catheter in the heart (Biorck *et al.*, 1950) or during cardiac surgery (Campbell and Reynolds, 1952), when frequent arrhythmias are seen due to direct stimulation of the heart, in one by the catheter and in the other by the surgeon.

Conduction Defects. The P–R interval increased by 0·02–0·04 sec. in six cases, by 0·05–0·09 sec. in three, and by 0·16, 0·22, and 0·29 sec. in a further three, in each of whom 2 : 1 heart block occurred.

Widening of the QRS complex by 0·02 sec. occurred in two cases, by 0·05–0·13 sec. in six, and there was at least a moderate increase in three others but its extent was hidden by S–T segment changes.

In all, these defects were present in 19 cases. They usually started during the first minute after injection of the diodone. They appeared to be entirely due to the diodone in 12, and partly due to it in another 5. However, all the severe and most of the moderate changes occurred in patients in the second half of the series who received quinidine and intravenous procaine.

Q–T Interval. It was seldom possible to measure the Q–T interval accurately due to overlapping of the T and P waves. It was not thought justifiable, therefore, to draw conclusions from the few where this could be done.

S–T Segment Deviation. S–T depression alone was present in 17 cases and elevation in another 10. It was 1 mm. or less in thirteen, between 1 and 2 mm. in ten, 3 mm. in one, and 10 mm. or more in three (Cases 4, 7, and 8; see later) where accurate measurement was not possible.

Twenty-four of the 27 patients were under anæsthesia, but the deviation appeared only after the injection in 18, usually during the first minute. In two of the three patients not under anæsthesia the deviation was first seen before the injection, though in both it increased afterwards.

Thus the diodone was responsible for these changes in most cases; but in some, another factor, which cannot always have been the anæsthetic, must have been at least partly the cause.

T Waves. Changes in the T waves appeared to a greater or less extent almost constantly both before and after injection of the diodone. Both TI and TIII tended to be smaller than normal before the injection. After it TI became still smaller in almost all cases where a change occurred, but after a few minutes tended to increase again; while TIII tended to increase in size throughout this period. These changes usually bore no relation to other electrocardiographic or to clinical changes.

P Waves. Changes in the P waves were less than those in the T waves and appeared to be of no significance.

Comparison with Clinical Changes

Clinical cause for anxiety was not present as frequently as might have been expected from a study of the electrocardiographic changes that occurred during the investigations. There was serious anxiety over the condition of the patient during three of the 75 angiocardiograms in addition to the one who died; two other patients from a later series who died are included here for discussion.

The following are summaries of these 6 patients, 3 of whom died.

Case 1 (P086). This girl, 5 years old, had dextrocardia and a complicated heart lesion, which probably included pulmonary stenosis. Her disability was moderate, and her cyanosis moderate

but increasing. Following injection of the diodone there was some increase in an S–T segment deviation that was normally present, but her clinical condition remained satisfactory until she collapsed in the ward half an hour after the injection. It was not possible to get a further electrocardiogram until she was recovering, and this continued to show only the slight increase in S–T deviation that had been present since the injection. More significant changes at the time of her collapse may have been missed.

Case 2 (P087), Fig. 1. This boy, 5 years old, had Fallot's tetralogy. His disability and cyanosis were moderate, and he had been having spontaneous attacks of dyspnœa and cyanosis. Under anæsthesia, before injection of the diodone, there was some difficulty in getting him to breathe; his cardiogram at this time showed a partial bundle branch block, which was still present at the

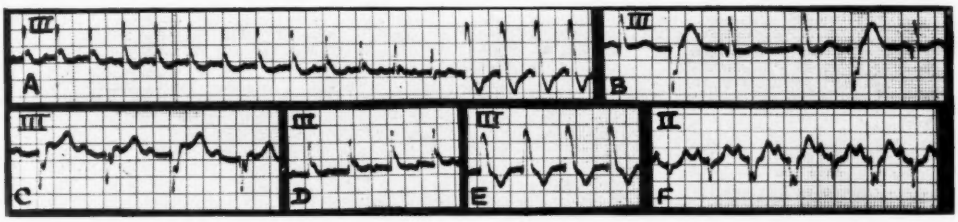


FIG. 1.—Case 2, lead III. (A) At the time of injection of the diodone, showing momentary disappearance of a bundle branch block and its reappearance in a more complete form at four and a half seconds after the start of the injection. (B) One minute after the injection, showing less bundle branch block, but now a partial A-V block and ventricular extrasystoles. (C) At seven minutes, showing 2 : 1 A-V block and a considerable change of axis. (D) At twenty minutes, still showing some bundle branch, but no A-V block. (E) At the time of his collapse at twenty-one minutes, showing a more severe bundle branch block. (F) Lead II three hours later, showing the bundle branch block becoming intermittent.

time of the injection. Immediately after this a series of abnormalities started due to depression of conduction—prolongation of the P–R interval, partial A-V block, and bundle branch block—and later frequent ventricular extrasystoles; but collapse only occurred twenty-one minutes after the injection, concurrently with the most complete bundle branch block he had yet shown. Clinical and cardiographic recovery started two hours later. A grossly distended stomach may have been an important factor here in causing cardiac embarrassment.

Case 3 (P130). This girl, 4 years old, had a single ventricle and pulmonary stenosis. Her disability and cyanosis were moderate. Following injection of the diodone both blood pressure and cardiographic changes were slight until she collapsed six and a half minutes later; simultaneously a partial A-V block developed and lasted for more than twenty minutes. Consciousness then soon returned. Excess bronchial secretions may have been a factor in this case.

Case 4 (O029), Fig. 2. This boy, aged 11 years, had Fallot's tetralogy. His disability was moderate and cyanosis slight, but he had been having attacks of unconsciousness. An ectopic rhythm was present for a few seconds immediately after injection of the diodone. Half a minute after the injection elevation of S–TIII began, with depression of S–TI, and was followed by widening of the QRS complexes. One and a half minutes later the patient collapsed, the previous cardiographic changes becoming more severe. An increasing arrhythmia led to ventricular tachycardia, flutter, and fibrillation, and the patient died.

Case 5 (O034), Fig. 3. This boy, aged 6 years, had pulmonary atresia. His disability and cyanosis were moderate. No significant change immediately followed the injection. Nodal rhythm appeared between one and a half and two minutes and was present most of the time until, at four minutes, there was a simultaneous fall in blood pressure and appearance of bundle branch block, with a partial A-V block for a short time at first. The blood pressure rapidly became unrecordable. Later multiple ventricular extrasystoles appeared, at first in short bursts of paroxysmal

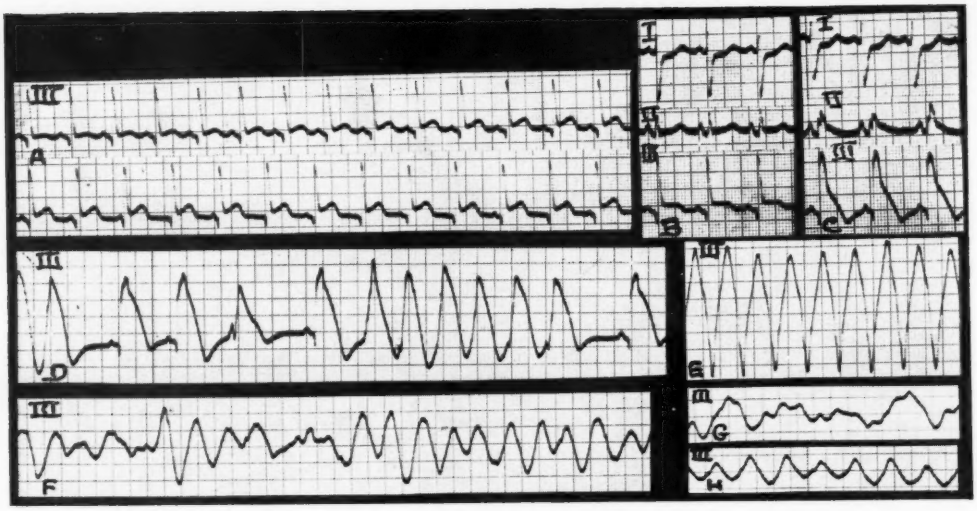


FIG. 2.—Case 4. (A) Lead III between 33 and 47 seconds after injection of the diodone, showing commencing elevation of the S–T segment. (B) and (C) Standard leads at one and a half and two minutes after the injection, showing depression of S–TI, increasing elevation of S–TIII and widening of the QRS complexes. (D)–(F) Lead III at two and a half, six, and eight minutes after the injection, showing severe bundle branch block and S–T elevation, ventricular tachycardia, flutter, and fibrillation. (G) and (H) Lead III two hours later, showing ventricular flutter and fibrillation still present, with a suggestion of auricular activity in (G).

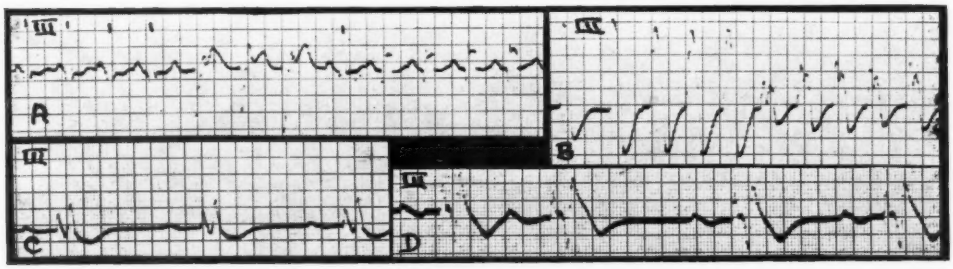


FIG. 3.—Case 5, lead III. (A) At four minutes after injection of the diodone, showing the onset of a changing bundle branch block. (B) At twenty-four minutes, showing a ventricular tachycardia that was present almost continuously from twelve and a half minutes after the injection until cardiac massage was abandoned. (C) and (D) Many minutes after cardiac massage had been abandoned and the patient was dead, showing recognizable auricular and ventricular complexes.

tachycardia, and then gradually disappeared leaving a slow irregular sinus rhythm, which was increased by methedrine until a partial A-V block slowed the ventricular rate once more. An irregular ventricular tachycardia appeared at twelve and a half minutes and persisted almost without a break up to the time that cardiac massage was abandoned.

Case 6 (P077), Fig. 4. This girl, aged 5 years, had transposition of the great vessels and pulmonary stenosis. Her disability and cyanosis were moderate, but she had had three attacks of unconsciousness. Her electrocardiogram was continuously abnormal from the time of the initial record shortly after the induction of anæsthesia. An ectopic and changing pacemaker was present most of the time before injection of the diodone, and frequently there was a variable A-V and an alternating bundle branch block. Sinus rhythm was re-established for the first minute after the

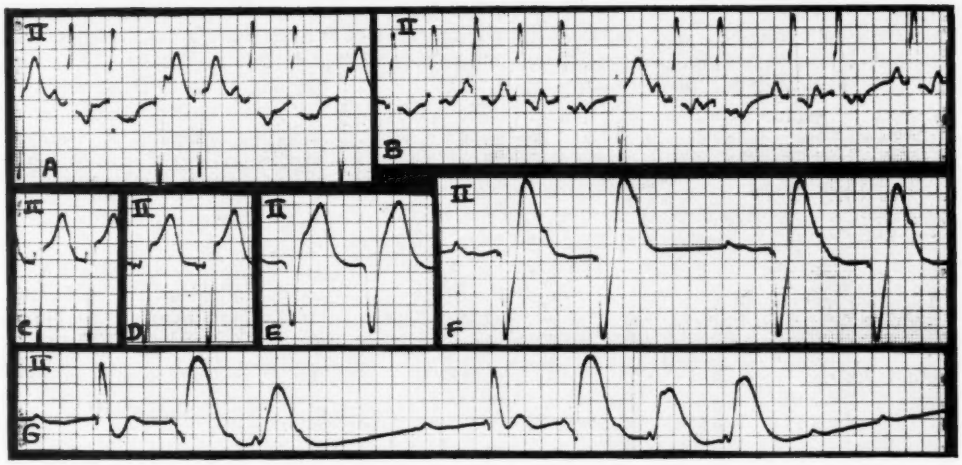


FIG. 4.—Case 6, lead II. (A) Before injection of the diodone, showing a changing pacemaker, 6 : 5 A-V block, and changing bundle branch block. (B) Between seven and ten seconds after the injection, showing the return of the sinus pacemaker. (C) and (D) At two and six minutes, showing slowing of a regular ectopic rhythm. (E) At the time of her collapse at eight minutes, showing a slow ventricular rhythm with greatly widened complexes. (F) At fifteen minutes, showing an auricular rhythm again, with a long P–R interval, 4 : 3 A-V block, and even wider ventricular complexes. (G) The final, grossly abnormal tracing after the patient was dead.

injection, but the partial A-V and bundle branch blocks remained until the former disappeared at two minutes: after this a regular ectpoic rhythm and bundle branch block persisted with a slowly decreasing rate until six minutes. At eight minutes the patient, whose condition had been satisfactory up to this time, collapsed, her cardiogram showing a slow ventricular rhythm. Thereafter an auricular rhythm returned intermittently with much delay in A-V and intraventricular conduction, while the rhythm became more irregular and the complexes more abnormal; and this continued long after the patient's death.

Three other patients showed severe electrocardiographic changes. One (Case 7) developed a severe S–T deviation and bundle branch block like that in Case 4 who died, but in this case it disappeared in little more than a minute (Fig. 5A). In another (Case 8) similar changes occurred

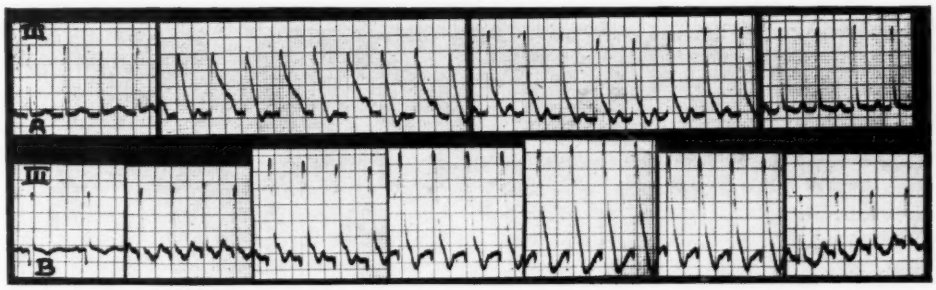


FIG. 5.—(A) Case 7, lead III at 40, 60, 90, and 120 seconds after injection of the diodone, showing a transient but severe bundle branch block and elevation of the S–T segment, and an odd, alternating obliquity of the latter. (B) Case 8, lead III, normally and at intervals of a few minutes while the patient was under anæsthesia before injection of the diodone, showing the appearance and disappearance of a bundle branch block and elevation of the S–T segment.

and resolved spontaneously while under anæsthesia before injection of the diodone without any clinical cause for anxiety (Fig. 5B). The third patient (Case 9) showed signs of a severe depression of both A-V and intraventricular conduction, and gave some anxiety due to a severe fall of blood pressure after injection of the diodone.

A fall in blood pressure was first reported to occur in this investigation by Robb and Steinberg in 1939 and shown graphically by Howarth (1950). It was an almost constant finding during the second half of the series in which this observation was made, and took place within a minute of the injection. The degree of the fall varied greatly, from a few millimetres to an unrecordable pressure. The systolic pressure fell more than 50 mm. in 5 of the 21 patients for whom figures are available, and in these the electrocardiographic changes were, on the average, twice as severe as in those in whom it fell less than this. These changes were of depressed conduction in four and S–T deviation in the fifth. They had been present in one before the injection and increased immediately after it; in the others they started between twenty and sixty seconds after the injection. Only in one of these patients did the clinical condition give rise to anxiety in any other way.

Thus a severe early fall of blood pressure was always associated with a very abnormal electrocardiogram, but usually without any subsequent cause for anxiety; while such a fall and immediate change in the electrocardiogram were not constant in those patients who later collapsed. Pressures were taken in four patients who collapsed: one had no early fall and one had only a slight fall, and neither of these showed early electrocardiographic changes; while two had severe early falls accompanied by considerable electrocardiographic changes.

One other patient caused some anxiety by persistent vomiting, which started about twenty minutes after the injection, and by a delay of about an hour in returning to consciousness. His cardiogram following the injection showed a moderate degree of S–T depression but this lasted only a few minutes.

The early abnormalities seen in patients whose clinical condition gave rise to anxiety were mainly those of a depressed conduction and to a lesser extent of S–T deviation. However, the initial change in all three patients who died was the appearance of an ectopic pacemaker; although in one it was accompanied by abnormalities that were more certainly pathological and in the other two it disappeared before more serious disturbances occurred. As this arrhythmia was seen for the first time after the injection in only one other case, it may have a greater significance in these circumstances than it usually has.

Cause of Clinical Changes

The diodone must be mainly responsible for the danger of this investigation, though other factors certainly add to the danger. The effects of the diodone may be exerted in several ways.

Peripheral vasodilatation probably causes the fall in blood pressure (Howarth, 1950) and unpleasant symptoms that immediately follow the injection, since the initial central effect of the diodone is to increase the amplitude of pulsation, at least of the isolated heart (Heathcote and Gardner, 1945; Weatherall, 1942).

Increase in vascular permeability leading to a direct toxic action on the tissues may cause its later effects. Such lesions have been shown in the brain after intra-carotid injection of diodone by Broman and Olsson (1949), and electro-encephalographic abnormalities were noted by Mannheimer *et al.* (1951) after intravenous injection in a number of cases where an overriding aorta was present.

Alternatively vascular spasm may be responsible; this has been shown to occur after intra-arterial injection (van der Linden, 1942), but there is no evidence that it follows intravenous injection. However, Mikulicich (1951) took electrocardiograms on rabbits during injection of foreign proteins to which they had been sensitized and recorded abnormalities that were remarkably similar to ours during angiocardiography. He believes these changes to be due to spasm of the coronary vessels and pulmonary arterioles, and permeability changes in the tissues. Diodone may, perhaps, produce similar effects in a sensitized subject. Certainly the risk of angiocardiography

in patients with an allergic tendency is generally agreed, and Sussman and Grishman (1947) even consider it inadvisable when there is a history of allergy among relations.

The bulk of the injection, its hypertonicity, and other non-specific effects are unlikely to be of great importance since they do not differ from those of other contrast media, and yet these substances produce different effects (Weatherall, 1942).

Where severe electrocardiographic changes precede the patient's collapse they suggest that the effect is directly on the myocardium or, in view of the frequent occurrence of pulmonary symptoms and pulmonary œdema, on the lungs through anoxæmia and consequent myocardial ischæmia. Where severe changes occur only at the time of the collapse a peripheral failure seems more likely, and this may have a direct peripheral, a reflex, or a cerebral origin. The essential lesion may vary from case to case or it may always be peripheral but sometimes accentuated by a preceding cardiac embarrassment.

It is usually considered that anæsthesia increases the risk of the investigation and should be avoided if possible (Carnegie, 1951), though Mannheimer *et al.* (1951) advocate it as reducing allergic and toxic reactions. Our results provide little evidence that it is an added risk, for the ectopic arrhythmias (probably due to cyclopropane) that were its common effect before the injection seemed of little consequence, and it did not appear to accentuate the more serious changes that followed the injection. But there can be no doubt of its danger if it allows anoxia to develop, and this may have been the cause of the more significant changes that occasionally preceded the injection, including those seen in Case 8.

Quinidine and intravenous procaine lessen ectopic arrhythmias, but these are less frequent after injection of the diodone than depression of conduction; this tends to be accentuated by these drugs, probably more so in a damaged heart (Uhley and Wilburne, 1948; Long *et al.*, 1949; Graubard *et al.*, 1948). They should, therefore, be given with caution.

The absence of any correlation between the electrocardiographic changes and the degree of cyanosis indicates that the presence of a dextroposed aorta or the degree to which it is overriding is unlikely to be a significant influence on the risk of the investigation. On the other hand there was a significant correlation with the degree of disability. The disability of those with pulmonary stenosis, who formed the majority of our patients, is due to an inability to increase their pulmonary blood flow, and this may be the most important condition predisposing to the appearance of electrocardiographic changes during angiocardiography and to the cardiac embarrassment that these changes often indicate.

The Value of Continuous Electrocardiography

Electrocardiography is especially helpful during angiocardiography before the injection of diodone has been given, when it may reveal changes—particularly those due to depressed conduction—that after the injection are likely to increase and to be followed by collapse and even death of the patient. On three occasions since this was recognized conduction defects have been present before the injection, and for this reason the injection was abandoned.

After the injection has been given the electrocardiographic changes, especially those that first appear or increase in severity more than two minutes after the injection, may provide a warning that all is not well, and so allow earlier efforts to be made to maintain or restore the blood pressure or resuscitate the patient; but changes may only appear at the time of the collapse.

Summary

Electrocardiograms taken during 75 angiocardiograms are described. Most of the patients had cyanotic congenital heart disease. Sixty per cent showed significant changes. These were most frequent in the younger, and least in the older and less disabled patients.

Ectopic arrhythmias were seen in about a quarter of the patients. They usually appeared to be due to the anæsthetic and were stopped on several occasions by the injection of diodone. Defects

of conduction were seen in about the same number but appeared to be due to the diodone, though they may have been accentuated by the quinidine and intravenous procaine given to reduce ectopic arrhythmias. S–T deviation was seen in about a third of the patients; it was usually due to diodone, sometimes to the anæsthetic, and occasionally to more obscure factors.

A fall in blood pressure was almost constant immediately after injection of the diodone, and simultaneous cardiographic changes were related to it in degree. Later a general collapse, bearing no close relation to the initial effects, might occur suddenly between two and thirty minutes after the injection, and might or might not be preceded by an abnormal electrocardiogram.

The lesion causing the collapse may be in the heart or lungs or brain, or may be peripheral. It may result from vascular spasm, perhaps as an allergic reaction, or from a direct toxic action on the parenchyma.

Electrocardiograms should be taken during this investigation in cases of cyanotic congenital heart disease. When abnormalities due to depressed conduction or S–T deviation are present and are not obviously due to an anoxia that can be quickly rectified, the investigation should be abandoned.

I wish to express my sincere thanks to Dr. Maurice Campbell for his help in the interpretation of the electrocardiograms and advice on the preparation of this paper. I also gratefully acknowledge the help I received from Mr. Ian Hill and Mr. Lawrence Whytehead, who performed the angiocardiograms, and from Mr. F. H. Muir, Senior Technician in the Cardiac Department, Guy's Hospital.

This paper is a summary of a thesis submitted and accepted for the degree of D.M. (Oxon), and I wish to thank the Regius Professor of Medicine for permission to publish it.

References

Broman, T., and Olsson, O. (1949). *Acta radiol.*, **31**, 321.
Biorck, G., Sylvan, T., and Lindbloom-Tillman, G. (1950). *Acta cardiol.*, **5**, 509.
Campbell, M., and Hills, T. H. (1950). *Brit. Heart J.*, **12**, 65.
——, and Reynolds, G. (1952). *Cardiologia*, (*in the press*).
Carnegie, D. M. (1951). *Brit. med. J.*, **1**, 1230.
Gordon, A. J., Brahms, S. A., Megibow, S., and Sussman, M. L. (1950). *Amer. J. Roentgenol.*, **64**, 819.
Graubard, D. J., Kovacs, J., and Ritter, H. H. (1948). *Ann. intern. Med.*, **28**, 1106.
Heathcote, R. St. A., and Gardner, R. A. (1933). *Brit. J. Radiol.*, **6**, 304.
Horger, E. L., Dotter, C. T., and Steinberg, I. (1951). *Amer. Heart J.*, **41**, 651.
Howarth, S. (1950). *Brit. med. J.*, **2**, 1090.
van der Linden, P. C. (1942). *Arch. int. Pharmacodyn.*, **67**, 14.
Long, J. H., Oppenheimer, M. J., Wester, M. R., and Durant, T. M. (1949). *Anesthesiology*, **10**, 406.
Mannheimer, E., Landtman, B., and Melin, K. A. (1951). *Cardiologia*, **19**, 337.
Mikulicich, G. (1951). *Allergy*, **22**, 249.
Robb, G. P., and Steinberg, I. (1939). *Amer. J. Roentgenol.*, **42**, 14.
Sussman, M. L. (1948). *Surg. Gynec. Obstet.*, **87**, 349.
——, and Grishman, A. (1947), in *Advances in internal Medicine*, Interscience, New York, **2**, 102.
Uhley, M. H., and Wilburne, M. (1948). *Amer. Heart J.*, **36**, 576.
Weatherall, M. (1942). *Brit. J. Radiol.*, **15**, 129.

THE LUNG VOLUME IN HYPERKINETIC STATES

BY

D. G. B. RICHARDS, A. G. W. WHITFIELD, W. M. ARNOTT, AND J. A. H. WATERHOUSE

From the Departments of Medicine and Medical Statistics, Queen Elizabeth Hospital, University of Birmingham

Received February 1, 1952

Previous publications from this department have defined the normal range of the total lung volume and its subdivisions (Whitfield *et al.*, 1950 *a*, *b*, & *c*) and the changes that take place in low output cardiac syndromes (Richards *et al.*, 1951). The present paper describes the results of study of the lung volume in hyperkinetic states.

The subjects selected for this investigation were patients suffering from anæmia or hyperthyroidism. Sharpey-Schafer (1944, 1945) and Brannon *et al.* (1945) have shown that in anæmic states the cardiac output is raised and similar changes were demonstrated in hyperthyroid subjects by Davies *et al.* (1924), Liljestrand and Stenstrom (1925–26), Robinson (1926), Burwell *et al.* (1929), Fullerton and Harrop (1930), Boothby and Rynearson (1935), and Gladstone (1936). The cardiac output of a small group of hyperthyroid subjects has been determined by cardiac catheterization in this department and in each case it has been found to be grossly elevated. Davies *et al.* (1924), Fullerton and Harrop (1930), and Boothby and Rynearson (1935) also showed that in hyperthyroidism the cardiac output returned to normal as the basal metabolic rate decreased following partial thyroidectomy.

Rabinowitch (1923) determined the vital capacity in nearly 200 patients suffering from hyperthyroidism and found that it diminished as the basal metabolic rate increased. With rates of plus 90–100 per cent the vital capacity fell to 42 per cent of its normal while with lower rates (plus 20–30%) the vital capacity was 79 per cent of its normal. Peabody and Wentworth (1917) found slight diminution in the vital capacity of 7 patients suffering from hyperthyroidism and 13 cases of anæmia. Lemon and Moersch (1924) found the vital capacity often reduced in hyperthyroidism but the reduction was unrelated to the degree of thyrotoxicosis.

Patients suffering from emphysema have not been included in this study because of the changes in lung volume associated with that disorder.

Methods and Results

The vital capacity and its two components the complemental and reserve air were measured in the usual way on a Benedict-Knipping spirometer. The functional residual air, and from it the residual air, was determined by the closed circuit constant volume hydrogen (or helium) dilution method described by McMichael (1939).

Ten patients suffering from hyperthyroidism were studied before treatment and again when their basal metabolic rate had returned to normal following partial thyroidectomy. The results obtained are summarized in Table I. The lung volume of nine cases of anæmia was also determined before treatment and again either after normal blood levels had been restored or a substantial improvement in their hæmatological state had been attained. The results are shown in Table II. Of the anæmic subjects three were suffering from pernicious anæmia, two from melæna due to peptic ulcer, two from anæmia due to uterine hæmorrhage, one from thrombocytopenic purpura, and one from macrocytic anæmia following jejuno-colostomy.

A statistical analysis of the findings in the ten thyrotoxic and nine anæmic subjects considered as one group is shown in Table III.

A striking parallelism will be seen between the hyperthyroid and anæmic subjects both showing before treatment an increase of 200–400 ml. in the functional residual air and residual air and a reduction of 200–300 ml. in the vital capacity and complemental air, the reserve air and total lung volume remaining virtually unchanged. Owing, however, to the relatively small numbers in each group these changes do not attain any high degree of statistical significance until all the subjects are considered together (Table III). The justification for grouping them together is the well founded assumption that before treatment they are both hyperkinæmic while after treatment their cardiac output is normal.

TABLE I

MEAN DIFFERENCES IN LUNG VOLUME OF 10 THYROTOXIC SUBJECTS BEFORE AND AFTER THYROIDECTOMY

Division of lung volume	Mean in hyper-thyroid state (litres)	Mean after thyroid-ectomy (litres)	Mean difference (litres) Hyperthyroid state minus after thyroidectomy state	Standard error of mean	t	P
Total lung volume	4·74	4·63	+0·11	0·13	0·85	0·42
Vital capacity	2·73	3·00	−0·27	0·11	2·69	0·02
Complemental air	1·81	2·01	−0·20	0·10	1·90	0·09
Reserve air	0·92	1·01	−0·09	0·07	1·38	0·20
Functional residual air ..	2·92	2·62	+0·30	0·12	2·66	0·03
Residual air	2·01	1·60	+0·41	0·13	3·16	0·01

TABLE II

MEAN DIFFERENCES IN LUNG VOLUME OF NINE ANÆMIC SUBJECTS BEFORE AND AFTER EFFECTIVE TREATMENT

Division of lung volume	Mean in anæmic state (litres)	Mean after effective treatment (litres)	Mean difference (litres) Anæmic state minus " normal " state	Standard error of mean	t	P
Total lung volume	4·91	4·91	0·00	0·11	0·01	0·98
Vital capacity	2·96	3·17	−0·21	0·08	2·58	0·03
Complemental air	2·01	2·22	−0·21	0·07	3·21	0·01
Reserve air	0·96	0·94	+0·02	0·04	0·33	0·75
Functional residual air ..	2·90	2·69	+0·21	0·15	1·43	0·19
Residual air	1·95	1·74	+0·21	0·15	1·39	0·20

TABLE III

MEAN DIFFERENCES IN LUNG VOLUME OF 9 ANÆMIC AND 10 THYROTOXIC SUBJECTS BEFORE AND AFTER TREATMENT

Division of lung volume	Mean before treatment (litres)	Mean after treatment (litres)	Mean difference (litres) before treatment minus after treatment	Standard error of mean	t	P
Total lung volume	4·82	4·76	0·06	0·08	0·70	0·49
Vital capacity	2·84	3·09	−0·25	0·07	3·69	0·002
Complemental air	1·91	2·11	−0·20	0·06	3·36	0·004
Reserve air	0·93	0·98	−0·05	0·04	1·07	0·30
Functional residual air ..	2·91	2·65	0·26	0·09	2·87	0·01
Residual air	1·98	1·67	0·31	0·11	2·95	0·009

An attempt was next made to ascertain to what extent these changes were correlated with the degree of anæmia as measured by the hæmoglobin percentage and the severity of thyrotoxicosis as indicated by the basal metabolic rate. The correlation coefficients obtained are shown in Tables IV and V from which it will be seen that in the thyrotoxic group the vital capacity and complemental air changes show no correlation and the functional residual air and residual air changes only a statistically insignificant positive correlation with the basal metabolic rate changes. Such a finding is hardly surprising and serves to confirm the impression that the degree of elevation of the basal metabolic rate above normal does not always agree with the severity of the thyrotoxicosis as judged clinically. In the anæmic group, however, there are positive correlation coefficients between the vital capacity and complemental air changes and the hæmoglobin percentage changes and negative correlation coefficients between the changes in the functional residual air and residual air and the hæmoglobin percentage change, all of which are statistically significant except in the case of the functional residual air.

TABLE IV

CORRELATION COEFFICIENTS BETWEEN LUNG VOLUME CHANGES AND BASAL METABOLIC RATE CHANGES IN HYPERTHYROID SUBJECTS

Total lung volume		+0·47
Vital capacity		+0·03
Complemental air		−0·05
Reserve air		+0·11
Functional residual air		+0·58
Residual air		+0·46
Significance levels	0·63	5%
	0·72	2%
	0·76	1%

TABLE V

CORRELATION COEFFICIENTS BETWEEN LUNG VOLUME CHANGES AND HÆMOGLOBIN PERCENTAGE CHANGE IN ANÆMIC SUBJECTS

Total lung volume		−0·42
Vital capacity		+0·77
Complemental air		+0·72
Reserve air		+0·35
Functional residual air		−0·61
Residual air		−0·71
Significance levels	0·67	5%
	0·75	2%
	0·80	1%

DISCUSSION

It is clear that in anæmia and thyrotoxicosis the vital capacity and complemental air are diminished and the functional residual air and residual air are increased, and in anæmic subjects these changes are correlated with the severity of the anæmia. The next question is what mechanism is responsible for these changes. It is natural to presume that the high cardiac output is responsible and in an endeavour to confirm this we determined the vital capacity before and after severe exercise in a series of ten normal subjects. There was no diminution after exercise except during the first 2½–5 minutes when dyspnœa and tachypnœa seemed undoubtedly responsible, and the transient increase in cardiac output associated with exercise does not appear to produce the diminution in vital capacity that is associated with the sustained hyperkinæmia of hyperthyroidism and anæmia.

In a previous publication (Richards *et al.*, 1951) we have shown that very similar lung volume changes occur in fully compensated " low-output " cardiacs such as the subjects of chronic rheumatic or hypertensive heart disease or coronary artery disease, and it is tempting to presume that in both

groups an increased volume of blood in the pulmonary circulation producing a stiff lung (lungenstarre) is responsible. However, Borden *et al.* (1949) have shown that in fully compensated mitral stenosis the volume of blood in the lungs is not increased and such an explanation is therefore open to doubt. Furthermore, though in hyperthyroidism the total blood volume is increased (Chang, 1931; Gibson and Harris, 1939) in anæmia it is reduced (Sharpey-Schafer, 1944, 1945), and it is difficult to believe that exactly the same lung volume changes could be produced by an increase in the volume of blood in the pulmonary circulation in two groups whose total blood volume differs in this way. It may be that prolonged hyperkinæmia produces an increase in the tissue fluid in the lungs (lungenschwellung) and that this is the responsible mechanism, but such an hypothesis seems quite impossible of proof.

All that can be said with certainty is that ventilatory efficiency is impaired in anæmia and thyrotoxicosis. How such impairment comes about is not understood.

Summary

The total lung volume and all its subdivisions have been determined in ten patients suffering from hyperthyroidism and nine patients with anæmia before and after effective treatment.

In hyperthyroidism and anæmia the vital capacity and complemental air are reduced and the functional residual air and residual air are increased. The total lung volume and reserve air are unchanged.

The mechanism underlying these changes is not understood and there is good reason to suppose that " lungenstarre " is not responsible.

In anæmic subjects the lung volume changes are closely correlated with the hæmoglobin percentage.

We are indebted to Professor Lancelot Hogben, F.R.S., for placing the facilities of his department at our disposal, to Miss Gwenda Griffith and Mr. A. C. Pincock for valuable technical assistance, and to Imperial Chemical Industries for a grant towards the expenses of this investigation.

References

Boothby, W. M., and Rynearson, E. H. (1935). *Arch. intern. Med.*, **55**, 547.
Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S. (1949). *J. clin. Invest.*, **28**, 1138.
Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A. (1945). *J. clin. Invest.*, **24**, 332.
Burwell, C. S., Smith, W. C., and Neighbors, de W. (1929). *Amer. J. med. Sci.*, **178**, 157.
Chang, H. C. (1931). *J. clin. Invest.*, **10**, 475.
Davies, H. W., Meakins, J., and Sands, J. (1923–24). *Heart*, **11**, 299.
Ebert, R. V., Borden, C. W., Wells, H. S., and Wilson, R. H. (1949). *J. clin. Invest.*, **28**, 1134.
Fullerton, C. W., and Harrop, G. A. (1930). *Johns Hopk. Hosp. Bull.*, **46**, 203.
Gibson, J. G., and Harris, A. W. (1939). *J. clin. Invest.*, **18**, 59.
Gladstone, S. A. (1936). *Proc. Soc. exp. Biol.*, N.Y., **34**, 587.
Lemon, W. S., and Moersch, H. J. (1924). *Arch. intern. Med.*, **33**, 136.
Liljestrand, G., and Stenstrom, N. (1925–26). *Acta med. Scand.*, **63**, 99.
McMichael, J. (1939). *Clin. Sci.*, **4**, 167.
Peabody, F. W., and Wentworth, J. A. (1917). *Arch. intern. Med.*, **20**, 443.
Rabinowitch, I. M. (1923). *Arch. intern. Med.*, **31**, 910.
Richards, D. G. B., Whitfield, A. G. W., Arnott, W. M., and Waterhouse, J. A. H. (1951). *Brit. Heart J.*, **13**, 381.
Robinson, G. C. (1926). *J. Amer. med. Ass.*, **87**, 314.
Sharpey-Schafer, E. P. (1944). *Clin. Sci.*, **5**, 125.
—— (1945). *Lancet*, **2**, 296.
Whitfield, A. G. W., Waterhouse, J. A. H., and Arnott, W. M. (1950, *a*). *Brit. J. Soc. Med.*, **4**, 1.
—— —— —— (1950, *b*). *Brit. J. Soc. Med.*, **4**, 86.
—— —— —— (1950, *c*). *Brit. J. Soc. Med.*, **4**, 113.

POTASSIUM AND THE CARDIOGRAPHIC CHANGES IN DIABETIC ACIDOSIS

BY

C. B. HENDERSON

From the Cardiovascular Department, General Hospital, Newcastle-upon-Tyne

Received June 6, 1952

This investigation was attempted in order to evaluate the cardiogram as a guide in estimating the level of potassium in the serum during, and when a patient is emerging from, diabetic acidosis. Shirley Smith and Hickling (1932) in a paper on cardiographic abnormalities in severe diabetes concluded that these changes represented mainly parenchymatous damage to the heart resulting from defective nutrition and that coronary disease, whether permanent or reversible, probably played a subsidiary role. Cardiographic changes in diabetic acidosis were described by Bellet and Dyer (1937) in a study of seventeen cases of coma and six of precoma; they listed lengthening of the Q–T interval, depression of the S–T segment, and inversion of the T wave as the most frequent findings and alteration of the QRS complex as infrequent. Other changes since described are: slight alteration in the character and amplitude of the P wave (Martin and Wertman, 1947); a prominent U wave (Ernstene and Proudfit, 1949); and cardiac arrhythmias (Bellet *et al.*, 1950). Ernstene and Proudfit (1949) did not find any constant lengthening of the Q–T interval in the cases they studied and pointed out that the commonly present U wave may cause apparent lengthening of the Q–T interval by partial fusion with the descending limb of the T wave.

The cause or causes of the cardiographic changes have been the subject of controversy among many authors. Because of the rapid development and regression of the abnormalities, Bellet and Dyer (1937) suggested that they were the result of a transient electrolyte imbalance. In the series of Martin and Wertman (1947) no close correlation was found between the levels of serum potassium and the depression of the S–T segment and prolongation of the Q–T interval. They thought that very low T waves were associated with low levels of serum potassium. Tarail (1948) found that the changes in the cardiograms of three out of five patients did not correlate with the degree of hypopotassæmia. Bellet *et al.* (1950) concluded that "The Q–T interval was a crude guide to the degree of hypopotassæmia, although the T wave and S–T changes were not reliable criteria of the degree of hypopotassæmia when comparisons were made in different patients; on the same patient, however, they correlated fairly well with the degree of hypopotassæmia."

Cardiographic changes similar to those found in dabetic acidosis, and associated with disturbances of potassium metabolism have provided further material for controversy concerning the role of serum potassium in their production. Steward *et al.* (1940), Stoll and Ninsnewitz (1941), and Perelson and Cosby (1949) described the cardiographic findings during the paralytic and recovery phases of familial periodic paralysis. Ernstene and Proudfit (1949) recorded the levels of potassium in the serum in a patient with Addison's disease who developed invertion of T waves, depression of S–T segments, and prominent U waves after being treated with desoxycorticosterone acetate to excess. Perkins *et al.* (1950) reported cardiographic findings in one case and McAllen (1951) in three of chronic diarrhœa with hypopotassæmia. The former described lengthening of the Q–T interval while the latter thought there was little if any Q–T change. Both of these authors concluded that there was correlation between the T wave and the S–T changes and the degree of hypo-

potassæmia, but McAllen could not find any correlation between the level of potassium in the serum and the slightly prolonged Q–T interval. He considered that in most previous publications the Q–T interval had been overestimated by including the U wave in the measurement.

Examination of the evidence shows that of the potassium deficiency diseases the most profound cardiographic abnormalities are found in diabetic acidosis. Low levels of potassium in the serum in diabetic acidosis were associated with more severe abnormalities of cardiographic form than the same potassium levels in idiopathic steatorrhœa, for example. The most significant difference in the alteration of potassium metabolism in these two diseases is the rapidity of the change, and this will be discussed later.

Material and Investigation

The present study is of ten consecutive cases of diabetic acidosis (four in coma and six in early coma) admitted into Newcastle General Hospital between September, 1950, and March, 1951. Eight patients were women, two were men, and their ages ranged between 12 and 59 years, with an average of 38 years. Two women died. Each case on admission had a blood sugar level above 275 mg. per 100 ml. and a carbon dioxide combining power below 22 volumes per cent.

Cardiogram, blood pressure, and venous blood for chemical analysis were taken in rapid sequence at intervals during and following the period of acidosis in each case. The carbon dioxide combining power, blood sugar and serum potassium levels were determined; the serum was separated within one hour of collection for the potassium analysis and always analysed by the same technician. The Jacobs and Hoffman (1931) method (normal range 16–20 mg. per 100 ml. was used for the potassium analysis and the accuracy of the method found to be $\pm 0{\cdot}5$ mg., using duplicate specimens.

Fifty-two cardiograms were taken on the Sanborn direct-writing cardiograph, with the patients supine in bed. The first cardiogram and blood specimen were taken within two hours of admission, but as several patients had been given large doses of soluble insulin subcutaneously before admission, records before treatment were not obtained in all. No patient was given digitalis or quinidine during the illness.

Examinations were performed post mortem on the two patients who died. Cardiac examination, before discharge from hospital in each of the patients who survived, showed no abnormality.

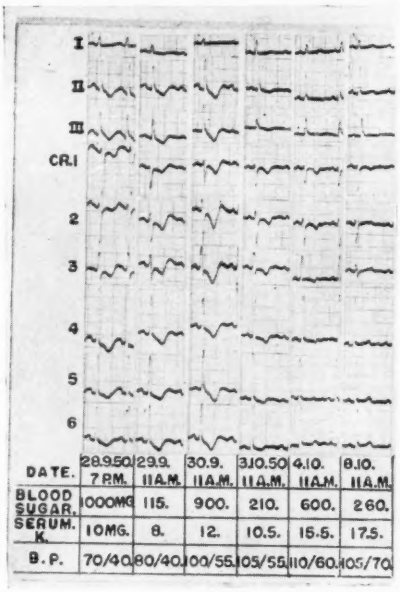
Presentation of Cases

The blood pressure, blood sugar and serum potassium levels are shown with each cardiogram in the illustrations, together with the times and dates.

Case 1 (Fig. 1). Mrs. G. B., aged 29 years, was admitted in early coma. On September 28, 1950, the serum potassium level was 10 mg. per 100 ml. and the cardiogram showed depression of S–T segments, inversion of T waves and prominent U waves. By October 8, the serum potassium was 17·5 mg. and the cardiogram almost normal. There was no correlation between the cardiographic and serum potassium changes in two of the six cardiograms taken.

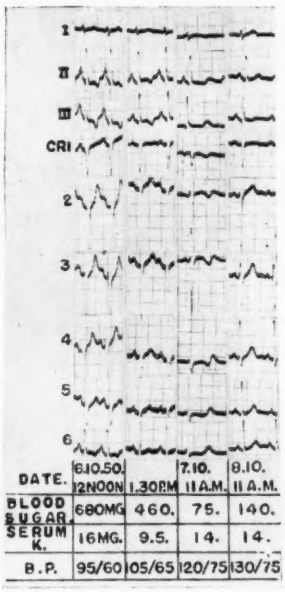
Case 2 (Fig. 2). Mrs. M. H., aged 35 years, was admitted in early coma. On October 6, 1950, the serum potassium was 16 mg. and the cardiogram showed tall and pointed P waves and inverted T waves in leads II and III and in CR6. T waves in leads CR2 to 4 were tall and narrow. One and a half hours later the serum potassium was 9·5 mg. and except for inverted T waves in leads II and III the cardiogram was normal. On October 7, the serum potassium was 14 mg. and the cardiogram showed paroxysmal nodal rhythm, inverted T waves and prominent U waves. On October 8, the serum potassium was unchanged and the cardiogram normal. The serum potassium and cardiographic changes did not correlate in this series.

Case 3 (Fig. 3). Mrs. I. D., aged 36 years, was admitted in early coma. On October 29, 1950 the serum potassium was 24·4 mg. and the cardiogram showed tall and pointed P waves, depressed S–T segments, tall and peaked T waves in leads CR1 and 4, and flat or inverted T waves in leads II, III, and CR6. Two hours later the serum potassium was 12 mg. and the cardiogram unchanged. On October 30, the serum potassium was 17 mg. and the cardiogram showed isoelectric S–T segments and flat T waves On October 31, the serum potassium was unchanged and the cardiogram had reverted to normal. There was no correlation between the serum potassium and the cardiographic changes in this series.



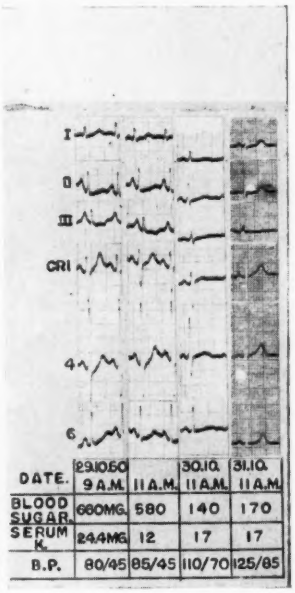
DATE.	28.9.50 7 P.M.	29.9. 11 A.M.	30.9. 11 A.M.	3.10.50 11 A.M.	4.10. 11 A.M.	8.10. 11 A.M.
BLOOD SUGAR.	1000MG.	115.	900.	210.	600.	260.
SERUM. K.	10MG.	8.	12.	10.5.	15.5.	17.5.
B.P.	70/40	80/40	100/55	105/55	110/60	105/70

FIG. 1.



DATE.	6.10.50 12 NOON	1.30 P.M.	7.10. 11 A.M.	8.10. 11 A.M.
BLOOD SUGAR.	680MG.	460.	75.	140.
SERUM K.	16MG.	9.5.	14.	14.
B.P.	95/60	105/65	120/75	130/75

FIG. 2.



DATE.	29.10.50 9 A.M.	11 A.M.	30.10. 11 A.M.	31.10. 11 A.M.
BLOOD SUGAR.	660MG.	580	140	170
SERUM K.	24.4MG.	12	17	17
B.P.	80/45	85/45	110/70	125/85

FIG. 3.

FIG. 1.—Diabetic acidosis. Case 1. S–T segments are depressed, T waves inverted and U waves prominent. Normal in 8 days.

FIG. 2.—Diabetic acidosis. Case 2. First tracing—tall and pointed P waves, inverted T waves in leads II, III, and CR6, and tall and narrow T waves in CR2 to 4. Third tracing—paroxysms of nodal rhythm, inverted T waves and prominent U waves. Normal in 3 days.

FIG. 3.—Diabetic acidosis. Case 3. Cardiographic abnormalities are similar to but not so severe as those seen in Fig. 2. Normal in 3 days.

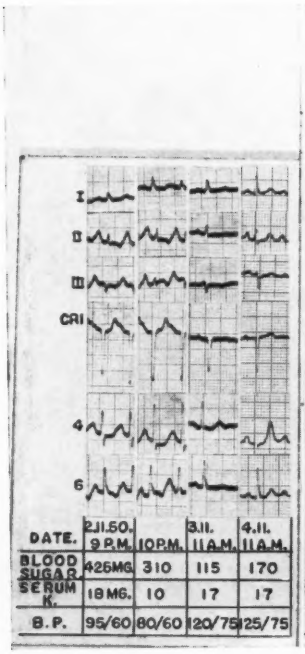
Case 4. Miss M. M., aged 27 years, was admitted in coma. On November 2, 1950, the serum potassium was 15 mg. and the cardiogram was normal except for prominent P waves. Three hours later the serum potassium was unchanged and the cardiogram showed S–T segment depression and small T waves. The next day the serum potassium had fallen to 13·5 mg. but the cardiogram had reverted to normal. On the following day the serum potassium also was normal. The cardiographic and serum potassium changes did not correlate in three of the five cardiograms taken.

Case 5 (Fig. 4). Mrs. F. F., aged 58 years, was admitted in coma. The serum potassium was 18 mg. and the cardiogram showed prominent P waves, depressed S–T segments, tall T waves in CR1 and inverted T waves in the limb leads and in CR4 and 6. One hour later the serum potassium had fallen to 10 mg. and the cardiogram was unchanged. Two days later the serum potassium and cardiogram were normal. The cardiographic and serum potassium changes did not correlate in three of the four cardiograms taken.

Case 6. J. S., aged 12 years, was admitted in early coma. The serum potassium was 21·5 mg. and the cardiogram showed depression of S–T segments, flat or inverted T waves, and prominent U waves. Three hours later the serum potassium had fallen to 12·5 mg. and the cardiogram was more abnormal. Two days later the serum potassium level and the cardiogram had returned to normal. The cardiographic and serum potassium changes did not correlate in two of the six cardiograms taken.

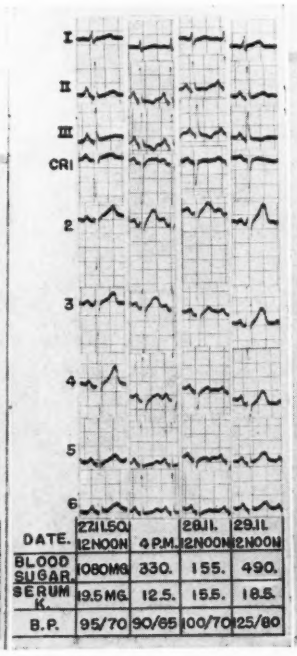
Case 7 (Fig. 5). Mrs. M. S., aged 34 years, was admitted in early coma. At noon on November 27, 1950, the serum potassium and the cardiogram were normal. Four hours later the serum potassium had fallen to 12·5 mg. and the T waves of the cardiogram were smaller. On November 28, the serum potassium had increased to 15·5 mg. but the amplitude of the T waves had further diminished and U waves were evident. On November 29, the serum potassium and cardiogram were normal. The cardiographic and serum potassium changes did not correlate in one of the four cardiograms taken.

Case 8 (Fig. 6). Mr. J. D., aged 39 years, was admitted in early coma. At 8 a.m. on December 26, 1950, the serum potassium was 13 mg. and the cardiogram showed auricular fibrillation with a ventricular rate of 150 a minute, depressed S–T segments and inverted T waves. Chest leads could not be taken because of the patient's tremor. Sinus rhythm returned the same day with the serum potassium at 15·5 mg. On December 30, the serum potassium level and the cardiogram were normal. The cardiographic and serum potassium changes did not correlate in one of the six cardiograms taken.



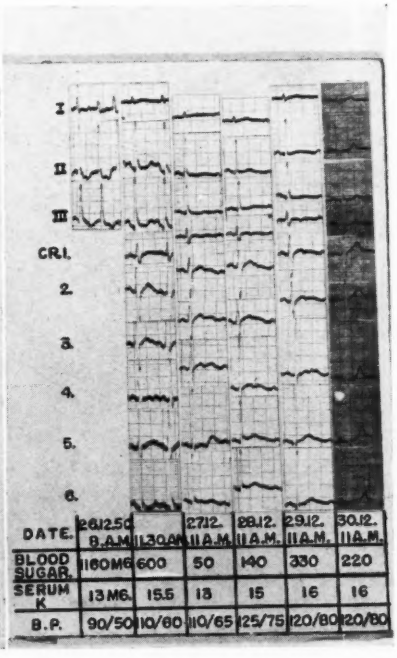
DATE.	2.II.50. 9 P.M.	10 P.M.	3.II. 11 A.M.	4.II. 11 A.M.
BLOOD SUGAR.	426 MG.	310	115	170
SERUM K.	18 MG.	10	17	17
B.P.	95/60	80/60	120/75	125/75

FIG. 4.



DATE.	27.II.50. 12 NOON	4 P.M.	28.II. 12 NOON	29.II. 12 NOON
BLOOD SUGAR.	1080 MG.	330.	155.	490.
SERUM K.	19.5 MG.	12.5.	15.5.	18.5.
B.P.	95/70	90/65	100/70	125/80

FIG. 5.



DATE.	26.12.50 8 A.M.	11.30 A.M.	27.12. 11 A.M.	28.12. 11 A.M.	29.12. 11 A.M.	30.12. 11 A.M.
BLOOD SUGAR.	1160 MG.	600	50	140	330	220
SERUM K.	13 MG.	15.5	13	15	16	16
B.P.	90/50	110/60	110/65	125/75	120/80	120/80

FIG. 6.

FIG. 4.—Diabetic acidosis. Case 5. Cardiographic abnormalities are similar to those seen in Fig. 3. Normal in 3 days.

FIG. 5.—Diabetic acidosis. Case 7. T waves are low or inverted in leads II, III, and the left chest leads. Normal in 3 days.

FIG. 6.—Diabetic acidosis. Case 8. First tracing—auricular fibrillation, S–T segment depression and inverted T waves. Second tracing—sinus rhythm. Normal in 5 days.

Case 9 (Fig. 7). Mrs. E. M., aged 50 years, was admitted in coma. At noon on January 23, 1951, the serum potassium was normal and the cardiogram showed auricular fibrillation with a ventricular rate of 130 a minute, wide QRS complexes, depressed S–T segments, and inverted T waves in the left chest leads. At 4 p.m. the cardiogram was unchanged but the serum potassium level had fallen to 13 mg. At 8 p.m. the serum potassium had further fallen to 10 mg. and the cardiogram showed considerable improvement and restoration of sinus rhythm. The cardiographic and serum potassium changes did not correlate in any instance.

The patient died two hours after the last cardiogram shown. At post-mortem examination the heart weighed 375 g. and there was no macroscopic evidence of heart disease. The coronary arteries were normal. Histological examination showed loss of muscle striation but no muscle necrosis or increased fibrosis.

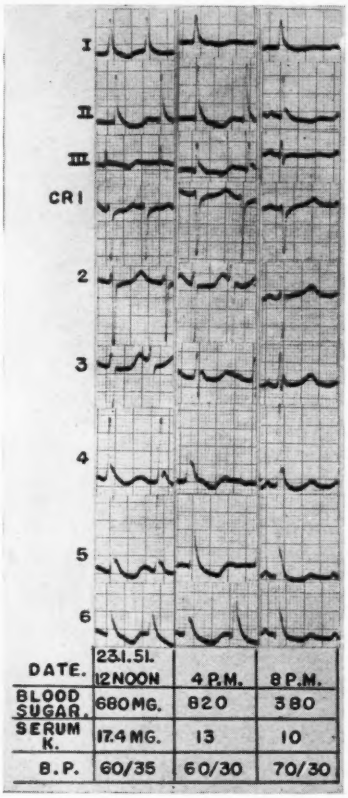


FIG. 7.—Diabetic acidosis. Case 9. First and second tracings—auricular fibrillation, S–T segment depression and flat or inverted T waves. Third tracing—sinus rhythm and larger T waves. Cardiogram much improved in 8 hours.

Case 10 (Fig. 8). Mrs. E. A., aged 59 years, was admitted in coma. At 7 p.m. on March 6, 1951, the serum potassium was 12 mg. and the cardiogram showed auricular fibrillation with a ventricular rate of 130 a minute, widening of QRS complexes, depression of S–T segments, and inversion of T waves. Three hours before death on March 10, 1951, the serum potassium was 11·5 mg. and the cardiogram normal. The cardiographic and serum potassium changes did not correlate in five of the ten cardiograms taken. At post-mortem examination the heart weighed 420 g. and the myocardium of the left ventrical showed multiple small areas of scarring. The coronary arteries were atheromatous but nowhere completely occluded. Histological examination showed diffuse fibrosis throughout the myocardium of the left ventricle. There was moist gangrene of the right foot and lower leg.

DISCUSSION

The present series of 10 cases again demonstrates the profound alterations that may occur in the cardiogram in patients during diabetic acidosis and when emerging from it. The cardiograms show that certain abnormalities occurred more frequently than in previous reports, e.g. cardiac arrhythmias, altered P waves, and prolonged QRS complexes; and a cardiographic pattern in uncomplicated diabetic acidosis has been brought to light. This pattern is seen in the first cardiograms in Figures 2, 3, and 4, and consists of tall and peaked T waves in the right chest leads and flat or inverted T waves in leads II and III and in the left chest leads; thus showing simultaneously

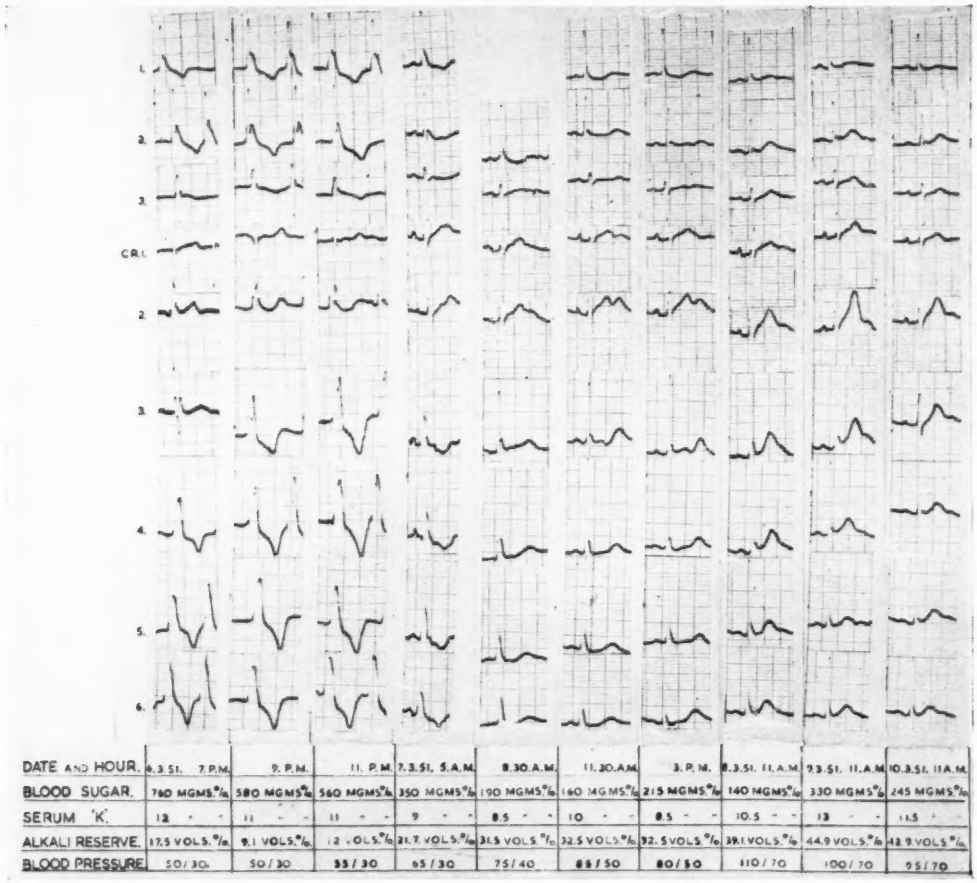


FIG. 8.—Diabetic acidosis. Case 10. First, second, and third tracings—auricular fibrillation, S–T segment depression and inverted T waves. Fourth tracing—sinus rhythm. Fifth to seventh tracings—prominent U waves. Normal in 5 days.

a combination of T wave abnormalities previously ascribed to a high concentration of potassium in the serum (tall T waves) and to a low concentration (flat and inverted T waves).

On the 42 occasions when abnormal features were present in the cardiograms, the degree of the abnormalities correlated with the levels of potassium in the serum in 21 instances and in 21 did not.

In general during the period when cardiographic abnormalities were increasing, the P wave, QRS complex, S–T segment, and T wave abnormalities occurred together, and the increase in size of the U wave occurred later. During recovery the P wave, QRS complex, and S–T segment reverted to normal first, then the T wave and finally the U wave. This period of recovery varied from 24 to 184 hours with an average of 68 hours in the patients who recovered. Of the two patients who died, one (Case 10) showed almost complete return to cardiographic normality in 88 hours, and the other (Case 9) considerable improvement in 8 hours. In general, the more pronounced the abnormality, the slower was the return to normal.

The Possible Influence of Intracellular Potassium on the Cardiogram

The oral or intravenous administration of potassium to a patient with diabetic acidosis will, after a variable time, produce improvement in an abnormal cardiogram. It would therefore appear that depletion of body potassium is of major importance in the production of the abnormalities. However, the data presented in this paper shows that in the 42 abnormal cardiograms taken, the degree of the abnormality correlated in only 21 instances with the level of potassium in the serum.

In the chronic diseases associated with a negative potassium balance such as nephritis and diarrhœa, in which a gradual fall in serum potassium concentration often occurs, the S–T segment and T wave changes appear to correlate roughly with the serum potassium levels (Perkins *et al.*, 1950, and McAllen, 1951). As the loss of body potassium in these diseases is slow it is probable that the extracellular potassium is in equilibrium with, and reflects the intracellular concentration. It is now recognized, however, that during the rapid phases of abnormal potassium metabolism such as occur in diabetic acidosis, the serum potassium does not always reflect the intracellular concentration. Danowski *et al.* (1947) showed that before treatment of diabetic acidosis the intracellular potassium concentration may be low, while the serum potassium is at normal levels, or even above. With recovery from the acidotic state, as the potassium in the cells increases, so the potassium in the serum falls sharply.

Darrow and Miller (1942) produced depletion of body potassium and cardiac lesions (necrosis of muscle fibres and replacement by fibroblasts) in rats by diets low in potassium, and by repeated injections of desoxycorticosterone acetate. They found that resting rats, on a low potassium diet, showed little change in the concentration of serum potassium despite the fact that muscle potassium was considerably reduced and the diminution of *muscle potassium* was an index of the incidence of cardiac lesions.

Perkins *et al.* (1950) reported a patient who showed potassium deficiency resulting from chronic diarrhœa who had an abnormal cardiogram. Oral and intravenous potassium chloride produced some improvement in the cardiogram which was, however, still abnormal shortly before death. The myocardium showed histological changes similar to those described in rats depleted of potassium. The authors concluded that the lesions in the heart were due to potassium deficiency analogous to those seen in experiments on animals. The relationship between the low intracellular potassium and the myocardial necrosis in the rats, and the cardiographic changes and myocardial necrosis in the case described by Perkins *et al.* (1950) may reasonably be linked together in implicating the intracellular potassium as the important agent in the production of the cardiographic changes. Additional circumstantial evidence for this is provided in the case of familial periodic paralysis recorded by Stewart *et al.* (1940). At the height of muscle paralysis the serum potassium was 11 mg. and the cardiogram was grossly abnormal. Two and a half hours later, after giving potassium by mouth, the function of the muscle improved, and the cardiogram improved, but the level of potassium in the serum was unchanged. This would suggest that the potassium content of the skeletal and cardiac muscle was rising while the concentration in the serum remained unaltered, and that the cardiographic improvement resulted from an increase in the intracellular concentration and was not influenced by the serum concentration.

Summary

Cardiographic abnormalities in ten cases of diabetic acidosis are described.

Cardiac arrhythmias occurred in four patients, three of whom showed transient auricular fibrillation and one showed transient nodal rhythm.

Tall and peaked P waves were present in four patients and were best seen in leads II and III. Subsequent tracings in each patient showed a rapid transition to normal P waves during recovery.

Transient widening and splintering of the QRS complexes occurred in leads I and II and the left chest leads in two patients, both of whom died.

Depression of the S–T segments were present at some time during the state of acidosis in eight patients.

Flat or inverted T waves in multiple leads were present in eight patients, six of whom also had depression of S–T segments.

U waves were abnormally large in six patients and small but easily identified in an additional three.

The Q–T interval could not be accurately measured in nine cases. In one (Case 7) in which accurate determination was possible, the corrected Q–T interval was normal.

A cardiographic pattern, not previously described, in diabetic acidosis, was seen in three cases and consisted of high peaked T waves in the right chest leads and flat or inverted T waves in the left chest leads.

Cardiographic recovery occurred within 24 to 184 hours in nine cases. Partial recovery occurred within 8 hours in one patient who died in coma.

There was no correlation between the level of the potassium in the serum and the degree of cardiographic abnormality in 21 of the 42 abnormal cardiograms taken.

The possible role of the intracellular potassium in the production of the abnormalities is discussed.

I wish to express my gratitude to Dr. George Richardson, physician in charge of the diabetic clinic, for his advice and for the ready access he gave me to patients under his care, and also to the staff of the Department of Pathology for the many biochemical estimations.

To Dr. W. G. A. Swan, I am particularly indebted for his encouragement and constructive criticism.

REFERENCES

Bellet, S., Dyer, W. W. (1937). *Amer. Heart J.*, **13**, 72.
——, Steiger, W. A., Nadler, C. S., Gazes, P. C. (1950). *Amer. J. med. Sci.*, **219**, 542.
Danowski, T. S., Hald, P. M., Peters, J. P. (1947). *Amer. J. Physiol.*, **149**, 667.
Darrow, D. C., Miller, H. C. (1942). *J. clin. Invest.*, **21**, 601.
Ernstene, A. C., Proudfit, W. L. (1949). *Amer. Heart J.*, **38**, 260.
Jacobs, H. R. D., Hoffman, W. S. (1931). *J. biol. Chem.*, **93**, 685.
Martin, H. E., Wertman, M. (1947). *Amer. Heart J.*, **34**, 646.
McAllen, P. M. (1951). *Brit. Heart J.*, **13**, 159.
Perelson, H. N., Cosby, R. S. (1949). *Amer. Heart J.*, **37**, 1126.
Perkins, J. G., Petersen, A. B., Riley, J. A. (1950). *Amer. J. Med.*, **8**, 115.
Smith, K. S., and Hickling, R. A. (1932). *Lancet*, **1**, 501.
Stewart, H. J., Smith J. J. (1940). *Amer. J. med. Sci.*, **199**, 789.
Stoll, B., Nisnewitz, S. (1941). *Arch. intern. Med.*, **67**, 755.
Tarail, R. (1948). *Amer. J. Med.*, **5**, 828.

THE EFFECT OF DIGITALIS ON THE NORMAL ELECTROCARDIOGRAM

BY

M. TILIAKOS

From the Cardiac Department of the London Hospital

Received October 22, 1952

With the advent of newer leads to the electrocardiogram it has become necessary to repeat the observations that have been made in the past on the cardiographic changes following digitalis administration in healthy subjects. The main object of this work has been to determine the lead or leads most susceptible to the effects of digitalis as well as the design of the deformity produced in the tracing. The need for the investigation has arisen from the common practice of giving digitalis to a patient considered to have heart disease before the electrocardiogram is recorded as part of a special examination. Confusion in diagnosis is specially likely if chest pain is included among the symptoms—a circumstance that allots more than ordinary importance to changes in the electrocardiogram.

Methods. The dosage of digitalis leaf was that customarily used in the continuous treatment of a patient needing it. It was, therefore, given in the first place as 2 grains (0·13 g.) daily and later increased to 3 grains (0·2 g.) daily. Rapid digitalization was not followed. Thirteen healthy medical students volunteered to take digitalis during a period of six to eight weeks when the total dosage was from 104 to 135 grains (6·9–9 g.). Digitalis was dispensed to each student when he attended the Cardiac Department to ensure accuracy in regard to the amount taken. A preliminary electrocardiogram was taken before the start of digitalis therapy and subsequent tracings were taken at intervals of four to ten days, and again after digitalis had been discontinued in order to discover the time it took the tracing to recover. The leads used included the four bipolar limb leads I, II, III, and IIIR (lead III during deep inbreathing) and the three chest leads CR1, CR4, and CR7. The tracing was recorded by an Elmqvist machine with the subject in the reclining posture and a standardization of 1 cm. from 1 mv. was strictly followed.

Results

No toxic symptoms appeared in any of the students during the period of medication. In the analysis of the results information was specially sought in regard to four problems. First, the smallest dose of digitalis that produced noticeable changes in the electrocardiogram. Secondly, the amount of digitalis that produced changes that could only be told by comparison of two records; this information has no great value in practice when only a single electrocardiogram is available at the time, and most papers on the cardiographic effects of digitalis deal only with the findings obtained from a comparison of two tracings. Thirdly, the particular deformity that signalled the earliest digitalis effect. Fourthly, the period needed for such changes to disappear and allow a return of the tracing to its normal design.

The results will now be discussed under two heads dealing separately with the lesser and the more noticeable cardiographic changes.

The Lesser Cardiographic Changes

Changes in the electrocardiogram that could only be told by a comparison of the tracing with one recorded before the start of digitalis therapy are calssified as lesser ones. They include an

alteration in the heart rate, heart rhythm, duration of the P–R and Q–T periods, form of the P wave, QRS complex, and T wave, and deformity of the S–T segment.

The heart rate. Many observers (Brams and Gaberman, 1931; Routier and Puddu, 1935) have reported a slowing of the heart rate by digitalis in most healthy subjects with sinus rhythm, but Pardee (1920) met this effect less frequently than changes in the height of the T waves. Other workers (Lassen *et al.*, 1937; Beers *et al.*, 1951) reported a slower pulse rate in from one-third to two-thirds of their cases.

In my series a change in the heart rate less than 10 a minute was not considered to be significant. In 7 cases the rate was reduced by 10 or more beats a minute, in 5 cases by 15 or more, and in 2 cases by 20 or more. As a rule such a reduction in the rate was induced by upwards of 42 grains (2·8 g.) of digitalis leaf given over a period of three weeks.

The heart rhythm. Although it is known that digitalis, especially in large doses, causes different forms of arrhythmia, these have seldom appeared in healthy subjects during digitalis medication (White and Sattler, 1916; Georgopoulos, 1934). Auricular premature beats, sino-auricular block, A-V dissociation, and paroxysmal auricular fibrillation are the commoner forms of abnormal rhythm to develop, but in the present series, when the subjects took some 135 grains (9 g.) within a period of 56 days, the rhythm remained normal in every case.

The P–R period. Slight prolongation of the P–R period by 0·01 to 0·04 sec. following digitalis given in daily doses of 15 to 60 grains (1–4 g.) for some days was present in 15 to 50 per cent of the cases reported by Cohn and Fraser (1913), Dieuaide *et al.* (1935), van Dyke and Li (1935), and Beers *et al.* (1951). McCulloch and Rupe (1921) found that lengthening of the P–R period in 9 out of 36 healthy children depended on the duration of the preceding diastole, being shorter after a long diastolic pause and longer after a short pause. Lassen *et al.* (1937) and Goldberger (1944) found lengthening of the P–R period in only a small number of their cases, while Cohn and Stewart (1929) found no change in six healthy subjects after a single dose of 12 to 15 grains (0·8–1 g.). None of my 13 cases showed an increase in the P–R period after taking upwards of 135 grains (9 g.) of digitalis over periods extending to 56 days.

The Q–T period. Shortening of the Q–T period is a common digitalis effect; it occurred in each of the 13 cases. It was calculated as a ratio of the Q–T period determined by Bazzett's formula. This lesser cardiographic change appeared along with shortening of the T wave, and it remained a little time after the return of the T to normal. The average Q–T ratio in my cases following digitalis was 0·80 as against 1·01 regarded as the average for healthy subjects. This finding agrees with the experience of other workers including Cheer and Dieuaide (1931), and Wiggers and Stimson (1927). White and Mudd (1929) found no alteration in the Q–T period in healthy subjects after digitalization when a dose of 30 to 45 grains (2–3 g.) was given in the course of seven to ten days.

The P wave. The effects of digitalis on the P wave of the electrocardiogram of healthy subjects have been variably described. Thus, unspecified changes were reported by Cohn and Fraser (1913), an increase in its size by Vacoel and Papapanajotou (1927), and a diminished amplitude by Routier and Puddu (1935). The P wave remained unchanged in my cases and this experience tallies with that of many other workers.

The QRS complex. Although a change in the electrical axis or in the amplitude of the QRS complex has been noticed by some authors in healthy subjects following digitalis therapy (Georgopoulos, 1934, others have not seen such changes (Beers *et al.*, 1951). No instance in the present series of 13 healthy students showed an alteration in either amplitude or duration of the QRS.

The S–T segment and the T wave. The more obvious deformity involving these components of the electrocardiogram is described under the more noticeable changes, and allusion here is only made to the earliest change that was only discernible by a comparison of the tracing with that recorded before digitalis therapy started (Fig. 1). When examined in this way depression of the S–T and lowering of the T wave took place within one or two weeks on digitalis when a dose of

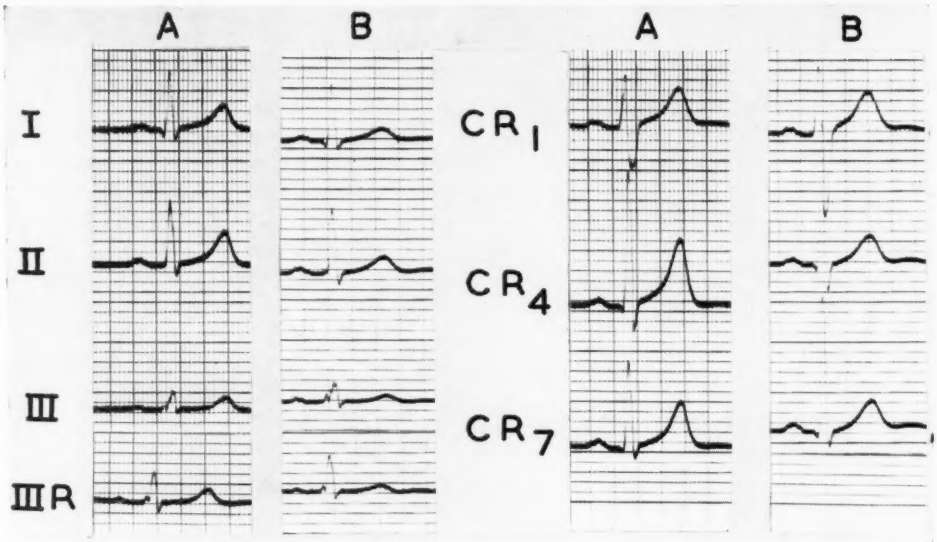


FIG. 1.—Lesser electrocardiographic changes following digitalis medication in a healthy subject (Case 7) who showed no more noticeable changes even after 107 grains (7 g.) of digitalis in 45 days. (A) is control tracing. (B) was taken after ingestion of 18 grains (1·2 g.) in 9 days; the Q–T period is reduced from 0·84 to 0·77 and the amplitude of the T wave is less than before in most leads.

from 14 to 30 grains (0·9–2 g.) had been given. A loss of height in the T wave preceded depression of the S–T in 10 of the 13 cases; in the other three cases both changes appeared together. Like the major changes, the lesser ones were also seen to best advantage in lead IIIR. As digitalization proceeded the earlier relationship between deformity of the S–T segment and the T wave became reversed so that at the end of digitalization, changes in the S–T were more noticeable than those in the T wave in all save three of the cases.

THE MORE NOTICEABLE CARDIOGRAPHIC CHANGES

It was Cohn and Fraser (1913) who first described depression of the S–T segment and of the T wave following administration of 6 grains (0·4 g.) of the digitalis leaf daily for a week. Such changes appeared in lead III at the start and thereafter in lead II and in lead I (Cohn *et al.*, 1915). The amount of digitalis necessary to cause deformity in the cardiogram has been estimated by various authors. Pardee (1920 and 1923) gave the effective dose as one-sixth or one-eighth of the therapeutic dose; Cohn and Stewart (1929) as about one-quarter of the lethal dose, and Bromer and Blumgart (1929) as half to two-thirds of the therapeutic dose. Marvin *et al.* (1925) found the cardiographic signs in 30 patients without heart disease from the administration of 22·5 grains (1·5 g.) per 100 pounds of body weight in the course of three days. Goldberger (1944) giving 30 grains (2 g.) of digitalis leaf in five days found that the cardiographic changes were constant irrespective of the pattern prevailing from any form of heart disease. Beers *et al.* (1951) obtained similar results and described the changes as preponderating in the left ventricular chest leads when the heart was in the transverse position and in the right ventricular leads when it was in the vertical position. Most authors have reported that actual inversion of the T wave does not result from digitalis medication in healthy subjects (Irving and Feil, 1941), and Dearing *et al.* (1943) thought that such gross changes indicated a myocardial lesion. Scherf and Boyd (1948), however, have

stated that inversion of the T wave does not always depend on the presence of existing myocardial damage on the grounds that the same changes occur when there is disturbance of intraventricular conduction. Friedberg (1950) has written that if obvious inversion of the T wave appears during digitalization, it is likely that the heart is diseased, for in health the changes are confined to the S–T segment. Coelho (1932) studying the effects of toxic doses of digitalis in dogs, healthy people, and patients with heart disease, found inversion of the T wave in the last, but never in the former two groups. Recently, Coelho and Borges (1952) re-examined the effects of digitalis on the electrocardiogram of healthy subjects and of patients suffering from different diseases which included gastric ulceration, bronchiectasis, Addison's disease, and avitaminosis; they reported that necropsy

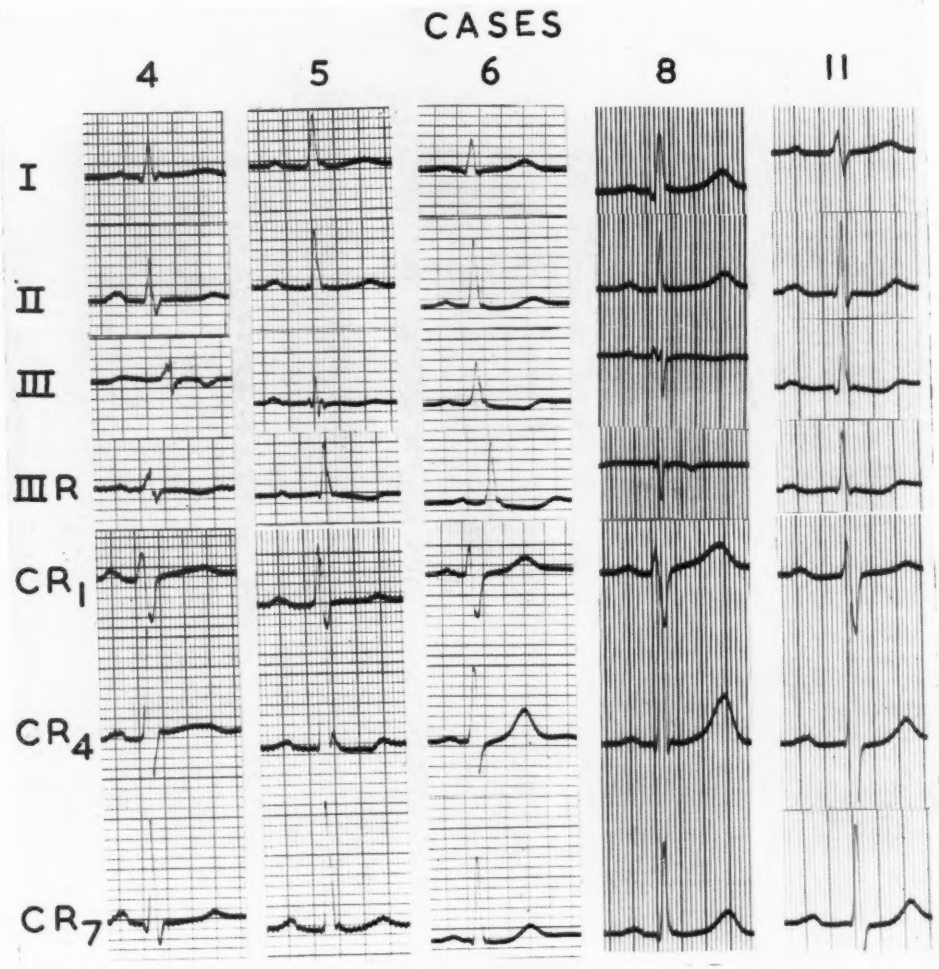


FIG. 2.—Noticeable electrocardiographic changes following digitalis medication in healthy subjects after a dosage of 104 to 135 grains (6·9–9 g.) in 42 to 53 days. S–T depression in IIIR is present in all and often in other leads as well. Significant lowering of the T wave is an additional feature of Cases 4 and 5.

in those where the T wave had been inverted showed atheroma of the coronary arteries, and they even suggested that digitalis should be given in this way to test the efficiency of the myocardium.

In the present investigation the selection of the first tracing showing signs regarded as noticeable changes was made on the pretence that the cardiogram under review was from a patient with cardiac pain; on this premise an unequivocal abnormality in the S–T segment or in the T wave was sought. Such changes were found in 11 of the 13 subjects during a period of digitalization which had lasted for six to eight weeks. In two students no obvious pathological signs could be identified in the single cardiogram (Fig. 1) after taking 106 grains of digitalis in 56 days in one, and 107 grains in 45 days in the other. No satisfactory explanation was found for the resistance of the heart to digitalis effects in these two instances; the one, aged 26, was tall and thin and the other, aged 24, was of average height and build. In the 11 cases showing changes, depression of the S–T segment was the deformity that first gave to the electrocardiogram its unequivocal abnormal appearance (Fig. 2). In eight the depression reached lower than the iso-electric level, while in the remaining three only a part of the S–T segment was depressed and not beyond the iso-electric line. The leads that showed such depression were considered and it was found that lead IIIR was the most sensitive lead in that it invariably showed the change either by itself or in combination with other leads, particularly III, II, and CR7; in three cases a depression of the S–T in III, remaining in IIIR, was the only significant change. In three students depression of the S–T segment was accompanied by an obvious lowering of the T wave in all leads, but in none did this deformity appear as a lone sign or as the initial major sign of digitalization. In this series S–T depression from digitalization appeared in both right and left chest leads, and the election of the side showing preponderant changes was not governed by the relative size of the R and S waves in CR1. Frank inversion of the T wave or even a flat T wave were not met with, but digitalis was discontinued in all 13 cases within eight weeks, and toxic doses were not employed.

These noticeable changes took place after the intake of from 105 to 135 grains (7–9 g.) of the digitalis leaf over a period of 42 to 56 days, an average dosage of 117 grains (7·8 g.) in 50 days.

The time taken for the significant changes to disappear from the cardiogram varied from 11 to 28 days, and the average period was 22 days.

Summary and Conclusions

Interest in the electrocardiographic changes produced by digitalis is not founded on the resultant changes in the heart muscle, but is directed solely to their recognition, so that they may not mislead in the diagnosis of a patient subject to cardiac pain who might at the time be taking digitalis. With this in mind digitalis was given to 13 healthy students and its effects watched in successive cardiograms.

Although lesser changes like shortening of the Q–T period, lowering of the T wave, and slight depression of the S–T segment appeared early and after the ingestion of 15 to 30 grains (1–2 g.) over a period of one to two weeks, they are of no great value in practice in that they are only discovered in a cardiogram when a control tracing is available for comparison. Such comparison showed that a loss of amplitude of the T wave usually preceded depression of the S–T segment, but after a time the latter became the more prominent deformity.

The more noticeable changes that could be told from an inspection of a single cardiogram appeared in all except two cases after a dosage of from 105 to 135 grains (7–9 g.) of digitalis given during 42 to 56 days. These changes consisted of depression of the S–T segment, and lead IIIR was foremost in showing the deformity, as a rule in conjunction with other leads but sometimes by itself. In three cases S–T depression was accompanied by obvious lowering of the T wave, but this was never found as the only cardiographic evidence of digitalization.

S–T depression in the cardiogram of a patient without hypertensive or valvular heart disease who is subject to chest pain and has received digitalis medication is evidence of a myocardial injury from coronary arterial disease provided the dose of digitalis has not exceeded 70 grains (4·6 g.) in five weeks, or if such treatment has been discontinued for a period of four weeks.

I wish to thank Dr. William Evans, Physician to the Cardiac Department of the London Hospital, for his help, and also the medical students who agreed to take part in the investigation.

REFERENCES

Beers, S. R., Regan, W., and Jensen, J. (1951). *Amer. Heart J.*, **41**, 114.
Brams, W. A., and Gaberman, P. (1931). *Amer. Heart J.*, **6**, 804.
Bromer, W. A., and Blumgart, L. H. (1929). *J. Amer. med. Assoc.*, **92**, 204.
Cheer, S. N., and Dieuaide, F. R. (1931). *Chinese J. Physiol.*, **5**, 217.
Coelho, E. (1932). *Arch. Mal. Cœur.*, **24**, 746.
—— and Borges, A. S. (1952). *Estratto Clinica Latina*, **2**, 1.
Cohn, A. E., Fraser, R. F., and Jamieson, A. R. (1915). *J. Exper. Med.*, **21**, 593.
——, and Fraser, F. R. (1913). *Tr. Internat. Cong. Med.* 1913, London 1914. Sect. VI, *Medicine*, Pt. II, 255.
——, and Stewart, H. J. (1929). *J. Clin. Invest.*, **6**, 53.
Dearing, H. W., Barnes, R. A., and Essex, J. H. (1943). *Amer. Heart J.*, **25**, 665.
Dieuaide, F. R., Tung, C. L., and Bien, C. W. (1935). *J. Clin. Invest.*, **14**, 725.
Friedberg, C. K. (1950). *Disease of the Heart*. Saunders, Philadelphia.
Georgopoulos, M. (1934). *Deutsch. Arch. Klin. Med.*, **176**, 348.
Goldberger, E. (1944). *Amer. Heart J.*, **28**, 370.
Grunbaum, F. (1931). *Ztschr. Klin. Med.*, **116**, 746.
Irving, M. L., and Feil, H. (1941). *Amer. Heart J.*, **22**, 683.
Lassen, K., Nuekirck, F., and Nielsen, N. (1937). *Amer. Heart J.*, **13**, 163.
McCulloch, H., and Rupe, A. W. (1921). *Amer J. med. Sci.*, **162**, 231.
Marvin, M. H., Pastor, B. R., and Carmichael, M. (1925). *Arch. intern. Med.*, **35**, 782.
Pardee, H. B. (1920). *J. Amer. med. Assoc.*, **75**, 1258.
——, (1923). *J. Amer. med. Assoc.*, **81**, 186.
Routier, D., and Puddu, V. (1935). *Arch. Mal. Cœur.*, **28**, 800.
Stewart, S. H., and Watson, R. (1938). *Amer. Heart J.*, **15**, 604.
Scherf, D., and Boyd, L. J. (1948). *Clinical Electrocardiography*. Heinemann, London.
Stewart, J. H., and Cohn, A. E. (1932). *Jour. Clin. Investig.*, **11**, 917.
Vacoel, J., and Papapanajotou, D. (1927). *Arch. Mal. Cœur.*, **20**, 24.
van Dyke, H. B., and Li, R. C. (1935). *J. Clin. Invest.*, **14**, 733.
White, P., and Mudd, S. (1929). *J. Clin. Invest.*, **7**, 387.
——, and Sattler, R. (1916). *J. Exper. Med.*, **23**, 613.
Wiggers, C. J., and Stimson, B. (1927). *J. Pharm. Exper. Therapy*, **30**, 251.

ISCHÆMIC HEART DISEASE AND PERIPHERAL OCCLUSIVE ARTERIAL DISEASE

BY

LAWSON McDONALD

From the Department of Medicine, the Middlesex Hospital

Received September 19, 1952

Angina pectoris and intermittent claudication are well known to occur together in the same patient. The analogy between angina pectoris and pain in the legs in intermittent claudication has been recognized since Brodie drew attention to it in 1846, some years after Heberden's description of angina pectoris as a separate disease entity (Heberden, 1772), and preceding Charcot's description of intermittent claudication in man (Charcot, 1859). Angina pectoris in this paper has been taken to include angina of effort, cardiac infarction, or any intermediate syndrome such as coronary insufficiency (Master, 1946). Intermittent claudication may be defined as limping or lameness, often accompanied by pain in the leg, coming on during exercise.

It has been said that the term angina pectoris should be reserved for patients in whom cardiac pain is due to coronary artery disease (Parkinson, 1951), and this relationship has been known to exist for a long time (Black, 1795). Coronary artery disease is certainly the commonest cause of this type of cardiac pain, and atherosclerosis accounts for about 95 per cent of cases of coronary artery disease (Plotz, 1948; Wartman and Hellerstein, 1948). Similarly, it is now acknowledged that atherosclerotic occlusive arterial disease is the commonest cause of intermittent claudication (Boyd *et al.*, 1949; Leriche, 1946; Lindbom, 1950; Luke, 1947), although this fact was temporarily obscured by Buerger's description of thromboangiitis obliterans in 1908 (Buerger, 1924; Weber, 1932). Subsequently, for many, intermittent claudication became synonymous with thromboangiitis obliterans, and if patients with the latter suffered from angina pectoris they were often considered to have thromboangiitis affecting the coronary arteries. Guillaume, amongst others, doubts whether thromboangiitis obliterans even exists as a separate disease entity (Guillaume, 1946); the authors cited above are at least agreed on its rarity. No proven case of it affecting the coronary arteries has been reported, and at least one authority on the pathology of arterial disease has never seen it (Dible, 1951).

Arteriosclerosis is widely acknowledged to be a generalized vascular disease (Allbutt, 1915; Aschoff, 1933; Dow, 1925); it might therefore be expected that two of its clinical manifestations, angina pectoris and intermittent claudication, might commonly occur together in the same patient. There have been numerous reports of such cases; some have been considered to be due to arteriosclerosis and others to thromboangiitis obliterans. But in view of what has already been written all that need be said is that they appear to have been examples of occlusive arterial disease affecting both the coronary and leg arteries.

The object of the present study was to determine how often angina pectoris and intermittent claudication, or the underlying occlusive arterial disease capable of producing either, occur together; this information is important in the treatment of a patient with either condition. The absence of angina pectoris or intermittent claudication in such patients will not exclude coronary or peripheral occlusive arterial disease capable of producing these symptoms, for either complaint may limit the

patient's activity to a degree less than that required to bring on the other. Therefore objective evidence of these conditions must be sought, even though they are not subjectively manifest.

Scope of Investigation

In this investigation 137 patients with occlusive arterial disease were studied; they presented with either angina pectoris or intermittent claudication. Eighty-seven patients with intermittent claudication were observed over a period of two years. Only those in whom the intermittent claudication was due solely to occlusive arterial disease were included; those with anæmia and coarctation of the aorta were excluded, also any in whom there was a possibility that arterial occlusion might have followed embolism. Fifty patients presenting during the same period with angina pectoris, either on effort or after cardiac infarction or as an intermediate syndrome between these two conditions were investigated. Patients whose cardiac pain might have been due to conditions other than coronary artery disease, such as luetic aortitis or severe anæmia, were excluded in the first instance.

In all patients presenting with intermittent claudication a full history was taken and clinical examination made; the blood pressure was estimated after at least fifteen minutes' rest in the recumbent posture. The following special investigations were performed: cardioscopy, blood count, blood Wasserman reaction, tonoscillography after exercise, and electrocardiography (usually leads I, II, III, unipolar chest leads V1 to V6, and augmented unipolar limb leads, VR, VL, and VF). Tonoscillography after exercise provides a useful diagnostic test of occlusive arterial disease affecting the legs (Ejrup, 1948; McDonald and Semple, 1952*a* and *b*); in some instances the diagnosis of occlusive arterial disease was further confirmed by arteriography or aortography. The patients who presented with angina pectoris were similarly investigated.

Results

As this investigation was made to determine the coincidence of coronary and peripheral occlusive arterial disease, 6 of the 87 patients who presented with intermittent claudication were excluded, because they were found to have aortic valvular disease. Some of these suffered cardiac pain and others did not; but, if present, its source could not be assumed to be occlusive arterial disease. In analysing the results two other patients were excluded because it was known that they had been referred because they had both conditions. All the patients seen with intermittent claudication were considered to have occlusive arterial disease due to atherosclerosis and/or arterial thrombosis, except one who had juvenile obliterative arteritis (Boyd *et al.*, 1949) or thromboangiitis obliterans. Of the remaining 79 patients presenting with intermittent claudication, 74 were men and 5 women. Twenty-three (29%) had angina pectoris in addition to intermittent claudication. In thirteen the onset of the intermittent claudication preceded that of the angina pectoris, in six the angina pectoris developed earlier. The remaining four started both symptoms at about the same time. The resting electrocardiograms were found to be normal in 48 of the 79 patients; the remainder were abnormal (Wood, 1950). An ischæmic pattern was present in 7, of whom five did not give a previous history of angina pectoris. Evidence of cardiac infarction was found in 8, and of these, three denied having had chest pain. There were 10 patients with a hypertensive pattern on the electrocardiogram. Left bundle branch block was present in 4; of these, two had angina pectoris and one hypertension, and no other heart disease was found clinically in the fourth, though the presence of left bundle branch block was considered to be suggestive, but not diagnostic, of ischæmic heart disease. There were 2 patients with right bundle branch block; one was hypertensive and the other had angina pectoris.

Therefore of the 56 patients with intermittent claudication who denied having angina pectoris eight (14%) showed electrocardiographic evidence of ischæmic heart disease, and one changes suggestive of its presence. A diagnosis of ischæmic heart disease was made either subjectively

(29%) or objectively alone (10%) in 31 of these 79 patients who presented with intermittent claudication (see Table I).

TABLE I

SEVENTY-NINE PATIENTS PRESENTING WITH INTERMITTENT CLAUDICATION

	No. of Cases	Percentage
Angina pectoris 23	31	39
Cardiographic evidence of ischæmic heart disease (no angina pectoris) 8		
No evidence of ischæmic heart disease found	48	61

Of the 50 patients presenting with angina pectoris, 44 were men and 6 women. Four (8%) suffered from intermittent claudication in addition to angina pectoris. One started to have angina pectoris before his intermittent claudication, and in one the intermittent claudication was the earlier of the two symptoms: the remaining two patients started to have these two complaints at about the same time. Eight (17%) of the remaining 46 patients without intermittent claudication, showed objective evidence of occlusive arterial disease of the legs. Thus, a diagnosis of occlusive arterial disease affecting the legs was made either subjectively or objectively in 12 of the 50 patients presenting with angina pectoris (see Table II).

TABLE II

FIFTY PATIENTS PRESENTING WITH ANGINA PECTORIS

	No. of Cases	Percentage
Intermittent claudication 4	12	24
Tonoscillographic evidence of occlusive arterial disease of the legs (no intermittent claudication) 8		
No evidence of occlusive arterial disease of the legs	38	76

The blood Wasserman reaction was found to be negative in all patients, except one on whom the test was not performed. The electrocardiographic findings on the patients presenting with angina pectoris are not reported here, as these patients were selected solely because they gave an unequivocal history of angina pectoris.

It is therefore apparent that coronary and peripheral occlusive arterial disease often exist together. In the present study the estimate of their coincidence is probably conservative, for the following reasons. Firstly, in seven patients with intermittent claudication who were among those longest under observation, evidence of ischæmic heart disease only developed some months after they were first seen, and was not found initially. Others still under observation may be expected to run the same course. Secondly, the frequency with which resting electrocardiograms are normal in patients with ischæmic heart disease is well known. And thirdly, with the method of tonoscillography used in this study about 5 per cent of symptom-free patients with occlusive arterial disease affecting the legs could be missed.

The way in which these 129 patients presented at hospital appeared to be quite arbitrary, for some of those presenting with intermittent claudication gave a history of having developed angina pectoris first, and vice versa. Therefore, for purposes of comparison, they have been divided into three groups.

Group 1. Patients with occlusive arterial disease of the legs, in whom no evidence of coronary artery disease was found (44 men and 4 women) 48
Group 2. Patients with occlusive arterial disease affecting both the coronary arteries and the legs (41 men and 2 women) 43
Group 3. Patients with coronary artery disease, in whom no evidence of occlusive arterial disease of the legs was found (33 men and 5 women) 38

Sex. Throughout the series of 129 patients there was a preponderance of men over women, in a ratio of over ten to one; a preponderance was similarly found in each of the groups (see above).

Blood Pressure. This was classified as follows: (1) *normal*, with a blood pressure of 140/90 or less; (2) *borderline systolic hypertension* with a systolic pressure over 140 mm. Hg; (3) *mild hypertension* with a diastolic pressure up to and including 110 mm. Hg and (4) *serious hypertension* with a diastolic pressure over 110 mm. Hg. Raised blood pressure was common (Table III). No significant difference was found in the distribution of hypertension amongst the three groups (males).

TABLE III
DISTRIBUTION OF LEVELS OF BLOOD PRESSURE

Group	Normal blood pressure (%)	Borderline systolic hypertension (%)	Mild hypertension (%)	Serious hypertension (%)
1	46	27	19	8
2	30	28	37	5
3	32	16	42	10

No woman had angina pectoris in the absence of hypertension, and only one out of six who presented with intermittent claudication had a normal blood pressure.

Age of Onset. The maximum period of onset was in the sixth decade. Those patients with intermittent claudication alone, or with both ischæmic heart disease and occlusive arterial disease of the legs, more often started to have symptoms in the second half of the sixth decade. Those with ischæmic heart disease alone showed a preponderance in the first half of the sixth decade. The earliest age of onset was in a man who started to have intermittent claudication at the age of 29 years; the latest age of onset was seen in two men who started to have intermittent claudication at the age of 77 years.

A *family history of cardiovascular disease* was frequently obtained in the present series of patients.

Obesity was not uncommonly found in the patients examined in the present study.

DISCUSSION

The results obtained in this study indicate the *frequent association of ischæmic heart disease and occlusive arterial disease of the legs*; thorough investigation reveals a much higher coincidence of the two conditions than has previously been recorded, although there has been an increasing awareness of the likelihood of the presence of ischæmic heart disease in patients with occlusive disease of the legs (Hines and Barker, 1940; Leriche, 1946; Rossier, 1946; and Samuels, 1950). The dramatic picture of angina pectoris often ending in death has perhaps clouded the less impressive peripheral arterial disease. In a recent paper on the natural history of coronary disease the presence of other vascular disease (and this was not limited to disease affecting the legs) was recorded in only 4 per cent of men and 7 per cent of women (Ryle and Russell, 1949).

Diagnosis and Pathogenesis. The not infrequent occurrence of ischæmic heart disease in youth was particularly realized when so many young men came under careful medical supervision during and after the second world war (French and Dock, 1944; Yater *et al.*, 1951); others had previously

found the same (Glendy *et al.*, 1937). In the present series of 50 patients presenting with angina pectoris 14 were under the age of fifty years. Similarly, intermittent claudication due to arteriosclerotic occlusive arterial disease is not uncommon amongst younger subjects (Boyd *et al.*, 1949); 17 of the 87 patients who were examined in this study, or over 19 per cent, started to have intermittent claudication under the age of fifty years. Thromboangiitis obliterans should not be diagnosed solely because of the comparative youth of some patients with occlusive arterial disease.

Prognosis. Although it is difficult to make an accurate prognosis in an individual patient with ischæmic heart disease, the probable prognosis in this group of patients is well known (Parker *et al.*, 1946; White *et al.*, 1943). The prognosis in patients with occlusive arterial disease of the legs will obviously be greatly influenced by the presence or absence of co-existent ischæmic heart disease. In one series 55 per cent were found to die within three years of their first attendance at hospital (Hines and Barker, 1940): these authors wrote that "the majority died in a manner that was suggestive of coronary thrombosis." The present series of patients with occlusive arterial disease of the legs has not been observed long enough to determine the prognosis of the group, nor can one say if it is representative. But the findings so far, especially the high incidence of ischæmic heart disease, coincide with previous views on the serious prognosis in this condition. The addition of ischæmic heart disease to intermittent claudication cannot be regarded favourably, but this is not true of the reverse position. Repeated attacks of myocardial ischæmia must eventually have some permanent effect on the heart muscle; if intermittent claudication only prevents these episodes by halting the patient before their onset, it would seem likely to be of benefit. Previous work (Blumgart *et al.*, 1950; Ravin and Geever, 1946; and Zoll *et al.*, 1951*a*) would suggest that the patient who can achieve a balance between sufficient activity to produce mild anoxæmia (to stimulate the development of collaterals) and activity that produces anoxæmia sufficient to cause permanent damage is fortunate. Coincident intermittent claudication might help to achieve this.

Common Factors in Coronary and Peripheral Occlusive Arterial Disease. The results in this study illuminate various problems common to both coronary and peripheral occlusive arterial disease. These include the sex incidence of occlusive arterial disease, the association of hypertension, particularly with angina pectoris in women, the age of onset of symptoms, also the frequent occurrence of a family history of cardiovascular disease and of obesity, among these patients. In this series and in others there is a striking preponderance of men among those who have occlusive arterial disease of the legs (Hines and Barker, 1940; Lindbom, 1950). This is also so in those with coronary occlusive arterial disease (Master *et al.*, 1939; Parker *et al.*, 1946; and White *et al.*, 1943). Angina pectoris is known to be rare in women in the absence of other heart disease; hypertension has been described as an important factor in its ætiology (Summers, 1948), although there is lack of agreement on its importance as such (Davis and Klainer, 1940; White *et al.*, 1950). All the women in the present series presenting with angina pectoris also had hypertension. Of the 6 women among 87 presenting with intermittent claudication, five had hypertension and one normal blood pressure. In the 77 men who were found only to have evidence of either ischæmic heart disease or peripheral occlusive arterial disease, the incidence of hypertension was not significantly different in either group, nor between these two groups and those who had both conditions. The frequency with which hypertension is found in patients with coronary artery disease is well known (Cassidy, 1946; Master *et al.*, 1939; and Zoll *et al.*, 1951*b*); there seems also to be a high incidence of hypertension, as defined in this study, among patients with intermittent claudication.

The level of blood pressure has been considered to play a part in the localization and severity of atherosclerosis; the higher incidence of coronary disease in hypertensive subjects has been suggested as evidence of this. The effect of gravity is added to that of systolic hypertension as a possible factor in the greater frequency of atherosclerosis in the arteries of the legs than the arms (Dock, 1946); the higher systolic pressure and steeper pulse wave which are found at the bifurcation of the aorta have been considered to correspond with the higher incidence of atherosclerosis there than in the thoracic aorta (Dock, 1946; Hamilton and Dow, 1939). The much thicker intima found in the coronary arteries than in arteries of similar diameter elsewhere in the body, and the

fact that these changes are greater in men than in women has been suggested to account for the sex difference in the incidence of coronary disease (Dock, 1946).

The maximum age of onset of symptoms found in the sixth decade in the present study corresponds with previous findings both in angina pectoris (Master *et al.*, 1939; Parker *et al.*, 1946) and in patients with intermittent claudication (Hines and Barker, 1940). The findings with regard to family history correspond with those of others in both angina pectoris (White, 1946) and intermittent claudication (Samuels, 1950). The common occurrence of obesity is of interest as it has been considered to be a factor in the incidence of at least some forms of arteriosclerosis (French and Dock, 1944), although this is not always completely accepted (Gregg, 1950).

Treatment. The results of this study are important with regard to the treatment of patients with angina pectoris or intermittent claudication; it should be realized that in treating either of these conditions the other may be liable to develop if it is not already present, or to become more severe if it is. Particularly before any surgical intervention is considered to relieve either peripheral or coronary occlusive arterial disease, a thorough examination of these patients should be undertaken; it may then be determined whether one symptom that limits the patient's activities should be replaced by another.

Summary

137 patients with occlusive arterial disease, presenting with either angina pectoris or intermittent claudication were studied; it was found that these conditions, or the underlying disease capable of producing them, commonly coexisted. Men were more often affected than women, and hypertension was frequently associated. Other common features in these patients are discussed, and the importance of a thorough examination is emphasized from the point of view of their management.

It is a pleasure to acknowledge the help and encouragement received from Dr. D. Evan Bedford and Professor Alan Kekwick throughout this work, and to thank them and other members of the Consulting Staff of the Middlesex Hospital for permission to study their patients. I wish also to thank Dr. John Goodwin for useful criticism and Dr. Robert Semple for much helpful discussion and for taking some of the tonoscillograms.

This paper includes part of a thesis submitted for the M.D. degree at Cambridge University, and I am indebted to Sir Lionel Whitby, the Regius Professor of Physic, Cambridge University, for permission to publish it.

References

Allbutt, C. (1915). *Diseases of the Arteries, including Angina Pectoris.* London, vol. II, p. 80.
Aschoff, L. (1933). In *Arteriosclerosis: A Survey of the Problem,* by Cowdry, E. V., New York, p. 14.
Black, S. (1795). *Mem. med. Soc. Lond.*, **4**, 261.
Blumgart, H. L., Zoll, P. M., Freedberg, A. S., and Gilligan, D. R. (1950). *Circulation*, **1**, 10.
Boyd, A. M., Ratcliffe, A. H., Jepson, R. P., and James, G. W. H. (1949). *J. Bone Jt. Surg.*, **31B**, 325.
Brodie, B. C. (1846). *Lectures Illustrative of Various Subjects in Pathology and Surgery.* London, p. 360.
Buerger, L. (1924). *The Circulatory Disturbances of the Extremities.* Philadelphia, p. 214.
Cassidy, M. (1946). *Lancet*, **2**, 587.
Charcot, J. M. C. (1859). *C.R. Soc. Biol. Paris, Série* **2, 5**, 225.
Davis, D., and Klainer, M. J. (1940). *Amer. Heart J.*, **19**, 185, 193, 198.
Dible, J. H. (1951). Personal communication.
Dock, W. (1946). *J. Amer. med. Ass.*, **131**, 875.
Dow, D. R. (1925). *Brit. med. J.*, **2**, 162.
Ejrup, B. (1948). *Acta med. scand.*, **130**, Suppl. 211.
French, A. J., and Dock, W. (1944). *J. Amer. med. Ass.*, **124**, 1233.
Glendy, R. E., Levine, S. A., and White, P. D. (1937). *J. Amer. med. Ass.*, **109**, 1775.
Gregg, D. E. (1950). *Coronary Circulation in Health and Disease.* London, p. 17.
Guillaume, A. C. (1946). Quoted in *Thromboses Artérielles* by Leriche, R., Paris, pp. 231, 268.
Hamilton, W. F., and Dow, P. (1939). *Amer. J. Physiol.*, **125**, 48.
Heberden, W. (1772). *Medical Transactions published by the College of Physicians in London*, **2**, 59.
Hines, E. A., and Barker, N. W. (1940). *Amer. J. med. Sci.*, **200**, 717.
Leriche, R. (1946). *Thromboses Artérielles. Physiologie Pathologique et Traitement Chirurgical.* Avec la Collaboration d'Ivan Bertrand, Paris, pp. 183, 259, 476.
Lindbom, A. (1950). *Acta radiol.*, Suppl. 80.
Luke, J. C. (1947). *Canad. med. Ass. J.*, **56**, 377.
McDonald, L., and Semple, R. (1952*a*). *Brit. Heart J.*, **14**, 91.
—— —— (1952*b*). *Proc. Roy. Soc. Med.*, **45**, 497.

Master, A. M. (1946). *N. York Med.*, **2**, 19.
——, Dack, S., and Jaffe, H. L. (1939). *Arch. intern. Med.*, **64**, 767.
Parker, R. L., Dry, T. J., Willius, F. A., and Gage, R. P. (1946). *J. Amer. med. Ass.*, **131**, 95.
Parkinson, J. (1951). *Lancet*, **2**, 695.
Plotz, M. (1948). *Amer. J. med. Sci.*, **215**, 91.
Ravin, A., and Geever, E. F. (1946). *Arch. intern. Med.*, **78**, 125.
Rossier, P. H. (1946). *Schweiz. med. Wschr.*, 37/38, 944.
Ryle, J. A., and Russell, W. T. (1949). *Brit. Heart J.*, **11**, 370.
Samuels, S. S. (1950). *Management of Peripheral Arterial Disease*. New York, pp. 175, 180.
Summers, V. K. (1948). *Brit. Heart J.*, **10**, 4.
Wartman, W. B., and Hellerstein, H. K. (1948). *Ann. intern. Med.*, **28**, 41.
Weber, F. P. (1932). *Proc. Roy. Soc. Med.*, **26**, 139.
White, N. K., Edwards, J. E., and Dry, T. J. (1950). *Circulation*, **1**, 645.
White, P. D. (1946). *Heart Disease*. New York, p. 483.
——, Bland, E. F., and Miskall, E. W. (1943). *J. Amer. med. Ass.*, **123**, 801.
Wood, P. (1950). *Diseases of the Heart and Circulation*. London, p. 83.
Yater, W. M., Welsh, P. P., Stapleton, J. F., and Clark, M. L. (1951). *Ann. intern. Med.*, **34**, 352.
Zoll, P. M., Wessler, S., and Blumgart, H. L. (1951*b*). *Amer. J. Med.*, **11**, 331.
——, ——, and Schlesinger, M. J. (1951*a*). *Circulation*, **4**, 797.

ABSTRACTS OF CARDIOLOGY

EDITED BY J. L. LOVIBOND

Sequelæ of Deep Thrombosis in the Lower Limbs. Follow-up Study of Patients Initially Treated by Conservative Measures. I. C. HÖJENSGÅRD. *Angiology*, 3, 42–47, Feb., 1952.

At the University Hospital, Copenhagen, the author examined 109 patients who had suffered thrombophlebitis in the legs as a complication of parturition 2 to 31 years previously. None had been treated with anticoagulants: all had been treated by strict immobilization of the legs. Statistical analysis of the findings shows that in 89% of the patients symptoms or signs attributable to thrombosis were still present, thus confirming the view now held that the condition should be treated by means other than immobilization.

Cecil Flemming

Diseases of the Superior Vena Caval System, with Special Consideration of Pathology and Diagnosis. J. R. VEAL and N. J. COTSONAS. *Surgery*, **31**, 1–12, Jan., 1952.

In this paper are discussed 137 patients with diseases of the great veins of the superior vena caval system. Of these patients 58 had a thrombosis of the axillary or subclavian veins, 50 an obstruction of the superior vena cava, and 11 an obstructed innominate vein. The remaining 18 had septic thrombophlebitis; in 14 of these, who were drug addicts, the cause was an infected injection of heroin.

C. G. Rob

Elastic Stockings in the Prevention of Pulmonary Embolism: a Preliminary Report. R. W. WILKINS, G. MIXTER, J. R. STANTON, and J. LITTER. *New Engl. J. Med.*, **246**, 360–364, March 6, 1952.

The authors quote previous observations that an external pressure of 10 to 15 mm. Hg applied to the leg decreases the effective vascular pressure and accelerates the venous flow. They refer to the tendency for older persons when confined to bed to develop venous thrombosis in the lower limb. With these observations in mind they have studied the effect on the incidence of pulmonary embolism of the wearing of elastic stockings by hospital patients.

There were no deaths from pulmonary embolism in a series of 2346 patients who wore elastic stockings continuously during their stay in hospital, although non-fatal emboli occurred in 2 cases. In a control group of 2395 patients who did not wear stockings, 4 had fatal and 12 non-fatal emboli. By contrast, clinical evidence suggesting local thrombotic disease in the legs occurred more often in the group who wore stockings (33 patients) than in the control group (27 patients). Patients with severe congestive cardiac failure and/or arterial disease of the lower limbs were excluded from both groups.

The authors conclude that elastic stockings do no harm, provided they are not applied too tightly, and that the results warrant further investigation into this method of prevention of pulmonary embolism.

J. F. Goodwin

Observations on the Surgical Treatment of Mitral Stenosis by Commissurotomy. T. J. E. O'NEILL, R. P. GLOVER, and C. P. BAILEY. *J. Amer. med. Ass.*, **147**, 1032–1033, Nov. 10, 1951.

This is a short summary from Philadelphia of the experiences of the authors in the operative treatment of 214 patients suffering from mitral stenosis. From a technical point of view they are very much in favour of division of the commissures with the knife rather than by "finger fracture." [Their results, when compared with those of the latter technique, scarcely justify this dogmatism.]

They classify their patients into five groups, varying from "Asymptomatic" to "Irretrievable," and confined their operations to those who fell within the three middle groups. Their results are assessed as follows: excellent, 89 (41·6%); improved, 70 (32·7%); unimproved, 29 (13·0%); dead (all causes), 26 (12·6%).

J. R. Belcher

Clinical and Physiological Correlations in Patients with Mitral Stenosis—V. B. M. LEWIS, R. GORLIN, H. E. J. HOUSSAY, F. W. HAYNES, and L. DEXTER. *Amer. Heart J.*, **43**, 2–26, Jan., 1952.

The area of the mitral valve and the degree of pulmonary vascular disease have been calculated from physiological data in 30 patients with pure mitral stenosis without evidence of active rheumatic carditis. From a hydraulic point of view, a valve area of 1·0 cm.², $\frac{1}{4}$ to $\frac{1}{6}$ normal, appears to be a critical one, for at that level of stenosis the pressure head needed to maintain a normal cardiac output approaches the plasma osmotic pressure. Probably from the stimulus of an increased pulmonary "capillary" pressure, a variable degree of vascular obstruction develops in patients when the mitral valve area becomes reduced to about 1·0 cm.² or smaller. This results in a lower cardiac output, which may protect the capillary bed from sudden increases in pressure.

The clinical picture in mitral stenosis can be explained in a large measure by the interplay of the degree of stenosis with the degree of pulmonary vascular obstructions. The combination of a narrow valve with only a slight increase in pulmonary arteriolar resistance is associated with predominantly respiratory symptoms, exer-

tional dyspnœa, hemoptysis, and paroxysmal nocturnal dyspnœa, the right ventricle not becoming dilated. The effect of a narrow valve and a high pulmonary arteriolar resistance appears to be additive in causing electrocardiographic evidence of right ventricular hypertrophy and roentgenographic signs of cardiac enlargement. The combination of a narrow valve and great increases in pulmonary arteriolar resistance is associated with severe dyspnœa, cardiac enlargement, and signs of right ventricular failure.

Most patients with mitral stenosis can be divided into four general categories by their signs, symptoms, and physiological adjustments.—[Authors' summary.]

Failure of Ligation of the Left Auricular Appendage in the Prevention of Recurrent Embolism. F. C. LEONARD and M. A. COGAN. *New Engl. J. Med.*, **246**, 733–735, May 8, 1952.

The authors point out that once a patient has had an embolism in an attack of rheumatic heart disease he may have a recurrence of the embolism at any time. The majority of emboli are thought to originate from the left auricular appendix, and therefore this structure has been amputated in the hope of preventing a clot from forming and spreading. It would appear, however, that this procedure is not adequate as a clot may well form within the cavity of the auricle proper.

The administration of dicoumarol and of anticoagulants over a prolonged period has proved to be the best treatment so far, and the authors consider that unless clots within the heart can be localized resection of the auricular appendix should be abandoned.

T. Holmes Sellors

Chronic Constrictive Pericarditis—I. Some Clinical and Laboratory Observations. V. A. MCKUSICK. *Bull. Johns Hopk. Hosp.*, **90**, 3–26, Jan., 1952.

Clinical details are given of 20 cases of constrictive pericarditis. The pressure curves obtained from the right ventricle were characterized by an early diastolic fall ("dip") in pressure followed by a rapid rise to a plateau at a high pressure level. This rapid rise in pressure in early diastole is presumably related to the reduced distensibility of the right ventricle as blood flows in from the auricle. A dip also occurred in the auricular pressure curve taken at the same moment, and in one case at operation an identical type of pressure record was obtained from the left ventricle. The pressure dip is closely related to the protodiastolic sound occurring in constrictive pericarditis. Tuberculosis plays a part in ætiology in some cases, but in others trauma may be important. The serum albumin level is occasionally low in constrictive pericarditis, but this may recover very rapidly after operation. Radiologically, dilatation of the superior vena cava with little cardiac enlargement is always suggestive, but localized constriction at the caval orifices was not found. Calcification was present in only half the cases. The condition may closely simulate mitral stenosis.

The results of pericardectomy were, in general, satisfactory. The only deaths that occurred were in patients over 55 years of age. *J. McMichael*

The Responsibility of the Physician in the Selection of Patients with Mitral Stenosis for Surgical Treatment. D. W. HARKEN, L. B. ELLIS, L. DEXTER, R. E. FARRAND, and J. F. DICKSON. *Circulation*, **5**, 349–362, March, 1952.

Examination of 35 normal hearts has shown that in addition to the ventricular and aortic leaflets there are two further small leaflets, the whole constituting a continuous veil round the circumference of the mitral orifice. In 85% of cases mitral stenosis is due to a rigid contraction of the leaflets without fusion of the chordæ tendineæ. Calcification is common in this type. In the remaining 15% an elastic funnel results from fusion of the chordæ. If the mouth of the funnel is turned towards the ventricular wall, ventricular contraction may close it during systole; if, however, the opening faces into the ventricular outflow tract, free regurgitation may take place. Calcification is rare in this group.

Finger-fracture valvuloplasty is regarded as the operation of choice for the first group, and may seem to restore the valve to normal. But there is no overlap of the leaflets, so that the valve would not remain competent if the ventricular pressure was high, as in aortic stenosis or hypertension. In the second group a valvulotome, fitted along the finger, may be needed to incise some of the chordæ.

Patients with mitral stenosis are classified as follows: (1) those without symptoms, who do not require operations; (2) those with dyspnœa on effort, who should be watched closely in case they pass into the next stage; (3) those with increasing dyspnœa and signs of pulmonary congestion (operation is urgently required for these, since they may die from pulmonary œdema); and (4) those with right ventricular failure, who should have had a valvulotomy earlier. The hazards are greater in these last, but operation should still be considered, as sometimes dramatic improvement follows. Active rheumatic carditis and severe aortic diseases are regarded as absolute contraindications, and mitral regurgitation as a relative contraindication. Extensive valvular calcification, auricular fibrillation, or a history of previous emboli are all considered to increase the risk.

C. W. C. Bain

Treatment of Subacute Bacterial Endocarditis with Aureomycin. C. K. FRIEDBERG. *J. Amer. med. Ass.*, **148**, 98–103, Jan. 12, 1952.

At the Mount Sinai Hospital, New York, 11 patients with subacute bacterial endocarditis were treated with aureomycin, 4 to 6 g. daily being given 6-hourly by mouth. In 6 of the patients the causal organism was *Streptococcus viridans* and in 2 *Strep. fæcalis*; no organism was isolated from 3 of the patients.

Aureomycin effected a cure in 2 of the cases due to *Strep. viridans* and in 2 of the 3 patients with negative blood cultures. Of the 6 patients with positive blood cultures who failed to respond to aureomycin 5 were subsequently cured with penicillin or a combination of antibiotics. In most of the cases administration of aureomycin was followed by clinical improvement, abolition of fever, and negative blood cultures, but the disease relapsed shortly after treatment was stopped.

This study supports the view that the action of aureomycin is mainly bacteriostatic as opposed to the bactericidal action of penicillin. It is concluded that aureomycin should not be used as a routine for the treatment of subacute bacterial endocarditis, but that its use, alone or combined with other antibiotics, is indicated in cases failing to respond to penicillin or infected with organisms resistant to penicillin. *C. Bruce Perry*

Myocardial Lesions in Subacute Bacterial Endocarditis. E. L. PERRY, R. G. FLEMING, and J. E. EDWARDS. *Ann. intern. Med.*, **36**, 126–137, Jan., 1952.

The myocardium was studied in 43 untreated cases of subacute bacterial endocarditis and in 9 cases treated with penicillin at the Mayo Clinic. Miliary infarcts in varying stages of development were found in 90% of all cases, and non-specific interstitial inflammatory lesions and perivascular lesions were found in 50% of the cases. These were regarded as embolic. In the treated group there was a greater tendency for the lesions to heal and the production of more chronic reactions. There appeared to be poor correlation between the myocardial lesions and the incidence of cardiac failure.

R. H. Heptinstall

Use of Quinidine in Treatment of Chronic Auricular Fibrillation. Results Obtained in a Series of One Hundred and Fifty-five Patients. E. H. YOUNT, M. ROSENBLUM, and R. L. MCMILLAN. *Arch. intern. Med.*, **89**, 63–69, Jan., 1952.

On the assumption that auricular fibrillation by itself may have deleterious effects on cardiac function, the authors have given oral quinidine—to which, they say, there are no contraindications except sensitivity—to 155 patients with chronic fibrillation, due in most cases to atheroma and rheumatic heart disease. In no fewer than 119 patients was sinus rhythm re-established in an average of 6 days with doses of 0·4 g. 4-hourly and a mean plasma concentration of 9 mg. quinidine per litre. No relation was found between age, cardiac failure, or duration of fibrillation and inability to revert; and since reversion invariably took place at a blood level of 8 to 12 mg. per litre it was not considered justifiable to increase dosage indefinitely in patients who did not respond. A therapeutic blood level was attained in a few hours, with cumulation over the first 3 days; when the drug was discontinued the blood level fell rapidly, and it seems probable that quinidine is destroyed in the body. The authors consider that about half the therapeutic dose is required for maintenance and may be given 6-hourly.

Toxic symptoms—chiefly gastro-intestinal and vestibular—occurred at a therapeutic blood level and may have been due to the rapidity of rise. It is suggested that the development of flutter is no reason for stopping quinidine, and the previous occurrence of emboli is regarded as an urgent indication for the drug; no embolic episodes occurred during treatment. Only 41 patients have so far been traced, and 6 of these have relapsed in an average period of 6 months after reversion.

A. Paton

Complete Functional Recovery after Coronary Occlusion and Insufficiency. A. M. MASTER and H. L. JAFFE. *J. Amer. med. Ass.*, **147**, 1721–1726, Dec. 29, 1951.

During the past 25 years the authors were called into consultation in 554 cases of acute coronary occlusion. Of this total 79 patients, of whom 35 died, were seen only in the acute attack, and for various reasons a satisfactory follow-up was not possible in another 63; these patients were excluded from the present investigation. An additional 141 patients were investigated in whom a diagnosis of acute coronary insufficiency had been made. The distinction between coronary insufficiency and occlusion was made on electrocardiographic findings, coronary insufficiency being diagnosed when the T-wave changes and the RS–T depression appeared early and returned to normal in several days or weeks, whereas coronary occlusion was diagnosed when the changes are more marked and more prolonged. The patients were followed up for a period averaging 6½ years (and ranging from 3 months to 29 years).

Of the 412 patients with coronary occlusion, 154 (37·5%) made a good recovery, and 115 (28%) made a satisfactory recovery but continued to have occasional effort angina.

Of the 154 patients who made a complete functional recovery, only 6 (4%) survived less than 5 years, and the total mortality in this group (19%) was less than half of that among the 115 patients who continued to have symptoms (47%); 25% survived more than 10 years, and 40% more than 5 years, 83% being employed during that time. Those who were less than 45 years old at the time of the attack did only slightly better than the older patients. The best prognostic guide after coronary occlusion thus appears to be the patient's symptoms rather than the objective findings. Whether an infarct was anterior or posterior did not appear to influence the future course. The prognosis following acute coronary insufficiency was better than that after coronary occlusion. Only 4% of these patients died, and more than half of them made a complete recovery.

The results as a whole indicate that most patients who survive an attack of coronary occlusion or insufficiency may be encouraged to lead fairly normal lives.

H. E. Holling

"Armchair" Treatment of Acute Coronary Thrombosis. S. A. LEVINE and B. LOWN. *J. Amer. med. Ass.*, **148**, 1365–1369, April 19, 1952.

In 81 cases of acute coronary thrombosis treated at home and at the Peter Bent Brigham Hospital, Boston, the patients were encouraged at the end of the first week of their illness to spend the greater part of each day sitting in a comfortable chair with their legs dependent; shock, marked debility, or cerebral vascular accidents were the only contraindications. The authors hold the view that this method reduces cardiac output, discourages pulmonary congestion, and reduces the incidence of thrombophlebitis and other complications. All the other methods of treatment usually employed in coronary thrombosis were also used.

In this uncontrolled series, in which there were 8 deaths (9·9%), the results were held to be satisfactory,

and the method appeared especially valuable in patients with congestive heart failure. The beneficial psychological effect of the manœuvre in reducing feelings of anxiety is also stressed. *J. W. Litchfield*

Indications for Bishydroxycoumarin (Dicoumarol) in Acute Myocardial Infarction. H. I. Russek, B. L. Zohman, A. A. Doerner, A. S. Russek, and L. G. White. *Circulation*, **5**, 707–711, May, 1952.

A series of 623 patients suffering from myocardial infarction were divided into two groups according to the history and the facts elicited at a physical examination carried out during the first 24 hours in hospital. In the first group were 338 " poor risk " patients, in whom one or more of the following were noted: evidence of previous myocardial infarction; intractable pain; extreme degree or persistence of shock; marked cardiac enlargement; gallop rhythm; congestive heart failure; auricular fibrillation or flutter, ventricular tachycardia or intraventricular block; diabetic acidosis; marked obesity; varicose veins; or evidence of previous thromboembolism. In the second group were 285 patients in whom none of these signs or symptoms was noted and these were classified as " good risk " patients. All the patients were treated conservatively. In the first group the mortality in hospital was 70% and the incidence of thrombo-embolism was 12·4%, compared with 3·5% and 0·7% respectively in the second group.

The authors suggest that it is pointless to subject the second group, which were mild cases, to the hazards of anticoagulant therapy for the sake [as they calculate] of a theoretically preventable mortality of about 1%.

R. S. Stevens

Chronic Cardiac Aneurysm. (Das chronische Herzaneurysma). B. Steinman and M. Elsaesser. *Helv. med. Acta*, **19**, 42–65, March, 1952.

This article is based on personal observation of 31 cases of aneurysm of the heart and includes a good review of the literature. The authors suggest that the condition is not so rare as is generally supposed and that its clinical, radiological, and electrographic signs should be more carefully looked for. A persistently raised S–T segment in the chest leads taken over the left ventricle (the most frequent site of aneurysm) is very suggestive of its presence. *G. S. Crockett*

Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease. C. B. Thomas. *Bull Johns Hopk. Hosp.*, **89**, 419–441, Dec., 1951.

At the end of the first 4 years a preliminary report is submitted on some 400 medical students of Johns Hopkins University who have been taking part in an investigation designed to elucidate the importance of some traits most frequently associated with the early onset of hypertension and coronary artery disease. This investigation included detailed heredity studies, studies of the cardiovascular system at rest and under stress, metabolic investigations, and personality studies. In no fewer than 93 out of 353 students there was a history of hypertension or coronary artery disease in at least one parent. In this group with a " positive " parental history there appeared to be a significant proportion of subjects with high resting blood pressure and heart rate, transitory tachycardia, and hyperreactivity to the cold pressor test and to exercise tests; 36% of 332 subjects showed evidence of hypercholesterolæmia.

[The hereditary factor in essential hypertension and coronary artery disease is now undisputed. It remains to be seen what, if any, significance can be attached to the finding of other " precursors " of hypertension and coronary atherosclerosis; the follow-up results in these (now apparently healthy) young subjects, extending over many decades, should be of some help.]

A. I. Suchett-Kaye

The Size of the Heart during the Course of Essential Hypertension. M. Kleinfeld and J. Redish. *Circulation*, **5**, 74–80, Jan., 1952.

The transverse diameter of the heart of 45 hypertensive patients was observed by teleradiography over a period of 5 to 20 years. It was found that 10 patients had normal measurement for 5 to 10 years, and 13 for more than 10 years. The degree of enlargement was assessed by comparing actual size with the predicted size as given in the tables of Ungerleider and Clark, and in some cases by fluoroscopy.

Progressive enlargement was seen in 24 patients, while in 18 the heart size remained stationary; 3 patients showed sudden increase in size followed by progressive enlargement. Cardiac failure might occur in patients with normal heart measurements, and marked enlargement might be present for 10 or more years with little functional impairment. Cardiac infarction might lead to sudden enlargement or be followed by no change in heart size. Reduction of body weight by 20 to 40 lb. (9 to 18 kg.) did not reduce the size of the heart.

The authors conclude that the size of the heart has, by itself, little value in deciding the prognosis in essential hypertension. *J. W. Litchfield*

The Treatment of Hypertension with the Kempner Diet and a Low-sodium Regimen. Clinical Observations on 600 Cases. F. Montoreano and J. Rabenko. *Prensa méd. argent.*, **38**, 2849–2856, Nov. 2, 1951.

This is an account from Buenos Aires of a study of 600 patients between the ages of 28 and 79 with essential hypertension, who were treated with Kempner's rice diet. The diet was given for periods varying from 2 weeks to 4 months; some patients took a modified Kempner's diet intermittently up to 2 years. The majority of patients refused the diet after a time. In about 90% improvement of symptoms was noted, but 60% complained of weakness. As regards the effect on blood pressure, the systolic pressure was reduced to normal in 69 (11·5%); it fell by over 50 mm. Hg in 156 (26%), 30 mm. Hg in 177 (29·5%), and up to 20 mm. Hg in 174 (29%); no change was noted in 57 (8%); and there was a rise in 36 (6%). The diastolic pressure was reduced to normal in 135 (22·5%); it fell by over 20 mm. Hg in 87 (14·5%), 15 mm. Hg in 174 (29%), and up to 10 mm. Hg in 168 (28%); there was no change in 144 (24%), and a rise in 27 (4%). The heart

size was determined radiologically in 106 cases, a reduction being observed in 35. The main change in the electrocardiogram consisted in a reduction in S–T depression. After the rice diet was stopped the blood pressure started to rise in about a fortnight, regaining its original level after a period varying between a few days and several months.

It is concluded that this method is effective in reducing the blood pressure without, however, modifying the course of the disease. *A. Schott*

Hypertensive Cardiovascular Disease. Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates. R. H. SMITHWICK. *J. Amer. med. Ass.*, **147**, 1611–1615, Dec. 22, 1951.

The author has attempted to determine the effect of standard lumbo-dorsal sympathectomy on the prognosis in hypertensive cardiovascular disease by comparing the mortality and survival rates in a series of cases treated surgically at the Massachusetts Memorial Hospital, Boston, with those in comparable cases treated medically at the same hospital or elsewhere. In classifying cases according to the severity of the disease, two methods of assessment are used, that of Keith, Wagener, and Barker (*Amer. J. med. Sci.*, 1939, **197**, 332) and that devised by the author. The former authors analysed a series of 219 cases of hypertension treated non-surgically, dividing them into four groups according to the severity of the changes in the optic fundus, to which they showed the prognosis to be closely related. These patients were followed up for a minimum of 5 years, and of the present author's series, 192 of the 296 patients treated medically had been observed for a similar period. The mortality rates among these 192 patients, when classified on the same basis, were found to bear a marked similarity to those in the earlier series, and the two series are therefore combined to provide a total of 411 medically treated cases, as against 538 surgically treated cases with a comparable follow-up period. The mortality rates in the latter show a very impressive reduction on those in the former in all four groups at 5 years, the difference being maintained to the end of the 5- to 10-year follow-up period. The most striking feature is the survival of 44% of surgically treated patients in Group 4 at the end of the period, compared with only 0·5% of those treated medically.

The author then classifies his whole series of 892 cases (596 treated surgically and 296 medically), in which the follow-up period ranged from 4 to 12 years, into four groups according to his own system, which takes account of various manifestations of hypertensive disease in addition to fundus changes. Again the comparison of mortality rates is greatly in favour of operation in all groups at 4 years and at the end of the follow-up period, the difference being most marked in the author's Groups 2 and 3. These groups include patients with any grade of fundus change and with cerebral, cardiac, and/or renal changes whose diastolic pressure is not above 140 mm. Hg and who are not suffering from severe renal damage, congestive heart failure, or the residuum of a cerebrovascular accident: the author considers that surgery is of real value in these two groups. For patients in his Group 1 (uncomplicated diastolic hypertension with a good prognosis), he concludes that surgery cannot as yet be justified on a statistical basis, whereas patients in Group 4—those with the most severe form of the disease—may benefit to a worth-while extent in the absence of nitrogen retention, which is considered an absolute contraindication to operation. Survival curves for the surgically and non-surgically treated cases in each group are given. *C. J. Longland*

Hypertension and the Surgical Kidney. A. D. PUPPEL and E. P. ALYEA. *J. Urol.*, **67**, 433–440, April, 1952.

The authors have studied the incidence and behaviour of hypertension coexisting with renal lesions in patients coming to nephrectomy and compared their findings with those in hypertensive patients without renal lesions.

In 23 of 67 patients with hypertension at the time of nephrectomy, which was performed for other reasons, blood pressure was normal two or more years after operation. This was most commonly seen after removal of a hydronephrotic kidney. The incidence of surgical renal lesions in hypertensive patients is only 2% and routine pyelograms are not, therefore, considered to be justified in hypertension. The incidence of hypertension is not significantly higher in patients admitted to hospital for surgical renal disease than in those admitted for other reasons. *J. Marshall Pullan*

Clinical Use of Cation Exchange Resins in the Treatment of Congestive Heart Failure. E. J. CALLAHAN, N. R. FRANK, H. KRAUS, and L. B. ELLIS. *Amer. J. med. Sci.*, **223**, 117–125, Feb., 1952.

The authors reaffirm the value of a cation-exchange resin (an ammonium–potassium cycle carboxylic resin) in the treatment of congestive cardiac failure. Patients receiving the resin were able to eat a more liberal diet, particularly as regards sodium, which was made unabsorbable by the resin. Mercurial diuretics could be reduced while the patients were taking the resin.

All toxic effects were manifested clinically, and the authors consider that elaborate laboratory studies are not necessary in following the progress of the patients. Gastro-intestinal symptoms, such as nausea, anorexia, vomiting, and constipation, were the commonest complications of treatment. Digitalis intoxication also occurred fairly often, but the reason for this remains obscure. The commonest electrolyte disturbances were those of hypocalcæmia and hypokalæmia, with a compensated acidosis. *G. S. Crockett*

IV Congrès National de Cardiologie will be held at Séville, Spain on May 7—10, 1953.

Any member of the British Cardiac Society wishing to attend should communicate with the Secretary of the British Cardiac Society.